TRAUMATIC SHOCK

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BY

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SURGICAL MONOGRAPHS

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TO

MY FELLOW WORKERS

IN BÉTHUNE AND

LONDON AND DIJON

1917–1918

PREFACE

Because of its mysterious onset and nature, traumatic shock has long suggested problems of unusual clinical and scientific interest. Its frequent occurrence in association with severe wounds renders a solution of these problems particularly important. But in spite of the large amount of attention which it has received, it has remained an enigma. I need only point to the numerous theories as to the cause and character of shock, to prove that there has been insufficient evidence to give definite answers to the questions which have been raised by it.

The phenomena of shock are seen typically after severe trauma. Thus, in railroad and industrial accidents associated with the crushing, tearing, and bruising of tissues, and also in extensive surgical operations, the phenomena may occur and prove a serious menace to the life of the individual. In warfare, shock occurs on an enormous scale, especially when wounds are made by fragments of shells, bombs, and grenades. Any tendency towards shock caused by a wound during battle is augmented by lack of immediate attention and by the consequent possibilities of continued hemorrhage and of exposure to wet and cold. The frequency of shock in the badly wounded has been noted again and again with each successive war. The opportunity for making observations on shocked men during the recent World War was widely recognized and efforts were made by French, English, and American observers to utilize this opportunity for obtaining further insight into the mysterious condition.

In the fall of 1916, a Committee on Physiology was established in the National Research Council, which had been organized to aid the United States government in case of need. Among the subcommittees of the Committee was one on Traumatic Shock. The members were a group of physiologists who had been studying the circulation and conditions influencing the various factors which determine the normal action of the circulatory organs. These physiologists early set to work to learn

the various methods by which shock could be reproduced in the laboratory, and the features of the state as they appeared under experimental reproduction.

In England, also, there was recognition of the importance of utilizing the opportunities offered by warfare to obtain further knowledge of the shock state. In February, 1917, the English Medical Research Committee issued "A Memorandum upon Surgical Shock and Some Allied Conditions" for the purpose of stimulating interest and securing new data. In this Memorandum were reviewed the observations by Dale and Laidlaw on the inductance of a shocklike lowering of the blood pressure by histamin and the observations of Bainbridge and Trevan on the production of shock by large doses of adrenalin. In both studies, a reduction of plasma volume was noted. The suggestion was offered in the Memorandum that human cases be examined for concentration of the blood by means of the hemoglobinometer and the hematocrit. Furthermore, certain practical hints regarding the prevention and treatment of shock were made and the hope was expressed that clinical observations might be reported to the Committee so that later memoranda might include both clinical and experimental results.

Although there were no centrally organized inquiries among French investigators, French surgeons were active in collecting clinical data from their personal experience; moreover, experimental studies were conducted in certain of the laboratories with the object of obtaining insight into and means of combating shock.

In the spring of 1917, it was my fortune to be a member of the Harvard University Hospital Unit which later became United States Base Hospital No. 5. Early in May of that year this organization was ordered to France for service in the British lines. With the expectation of having opportunity to study shock cases in forward hospitals, I accompanied the Unit and during the stay in England, before crossing the Channel, I spoke to the Secretary of the Medical Research Committee, then Dr. Walter M. Fletcher, regarding the interest of the group of American physiologists in the shock problem and my desire to obtain more direct knowledge of shock as it appears in human cases. He informed me that Colonel T. R. Elliott, long an acquaintance of mine, was the representative in France of the Medical Research Committee and that he would doubtless aid me in every way possible to obtain the favorable opportunity which I desired.

My thanks are due to Sir Walter M. Fletcher and to Colonel T. R. Elliott for their unfailing interest and their help in promoting the work

which was planned. Shortly after my arrival in France, I was separated from Base Hospital No. 5 and stationed with a group of surgeons, under command of Lieutenant-Colonel J. B. R. Winder at Casualty Clearing Station No. 33 of the British Expenditionary Force, then at Béthune. From about the first of July until the last of October, 1917, I had the advantage of being associated there with Captain John Fraser, and Captain A. N. Hooper and at times with Captain E. M. Cowell, all experienced surgeons and keenly interested in the phenomena of shock. Furthermore, we were serving under Colonel Cuthbert Wallace, later Major-General Sir Cuthbert Wallace, who was as eager as any of us to secure further knowledge of shock and who helped and encouraged us in our efforts.

In August, 1917, Professor W. M. Bayliss, who had previously published an important paper on substitutes for blood in raising a low blood pressure, and who, under the Medical Research Committee, was continuing in London studies on shock and hemorrhage, was sent to Béthune by the Committee to examine shock cases in coöperation with the group there and to confer with us regarding clinical results which had already been obtained. On the return of Professor Bayliss to London, there was formed under the Medical Research Committee a "Special Investigation Committee on Surgical Shock and Allied Problems." Professor A. N. Richards, of the University of Pennsylvania, who arrived in London shortly afterwards, began, in coöperation with Dr. H. H. Dale, to test some of the suggestions which had been offered on the basis of the studies at Béthune. Professor Richards and I were the American members of the new Committee and helped to keep the American and the English groups each acquainted with the other's progress.

On leaving Béthune in late October, 1917, I was sent to London where I remained for three and a half months. There I had the chance of working experimentally on ideas arising from the clinical studies at Béthune. The experimental work was done in coöperation with Professor Bayliss. It is a pleasure to express my gratitude to him for the many kindnesses which he showed me and for the hospitality of his laboratory which he so generously granted.

In April, 1918, at the suggestion of Brigadier-General J. M. T. Finney, the Chief Surgical Consultant of the American Expeditionary Force, Lieutenant-General M. W. Ireland placed me in charge of a laboratory of surgical research in association with the Central Medical Department Laboratory of the American Expeditionary Force at Dijon,

France. Under the direct command and the favoring interest of Colonel J. F. Siler, a group, which finally included Major H. O. Robertson, Lieutenant Joseph C. Aub, and Lieutenant McKeen Cattell, there continued observations on the nature of shock and on methods of treating it. Every week during the summer of 1918, we were engaged also in teaching the principles of treatment to medical officers who later became members of shock teams in forward hospitals. In the shock wards of such hospitals, each member of our group had service, at one time or another, during active military engagements. In the fall of 1918, a conference with French surgeons gave us closer acquaintance with their work and point of view.

Meanwhile, during the summer of 1918, further clinical studies were being prosecuted in the British service, especially the important studies of Keith on blood volume in shock; and laboratory research was continuing both in England and in the United States.

The activities in American, English, and French laboratories and hospitals, above outlined, have yielded a considerable body of new knowledge regarding factors which are concerned in shock. This has naturally afforded new insight into the mystery of the condition and into the most effective mode of treating it. The evidence thus accumulated has not before been formally gathered together. It is my hope that in the pages which follow I may succeed in presenting the new facts in a way which will bring out clearly what has been learned in addition to what was known before.

In previous treatises on shock, a large amount of space has commonly been devoted to the theories of shock which various investigators have enunciated and supported by argument and experiment. The tendency to theorize is always strong when available facts fail to account for the phenomena which are observed. It is wise, however, in the presence of a complex condition, to avoid the promulgation of theories, so far as possible, until a sufficient amount of evidence has been accumulated to justify a grouping of the facts in a theoretical scheme. Accordingly, in the present exposition of the subject, I have laid especial stress on the facts of clinical observation. These facts have been such as to require experimental analyses, and in so far as studies on lower animals have offered direct explanation of the clinical phenomena, the results of experimental study have been utilized.

After presenting and discussing the clinical phenomena of shock, I have considered the theories which have been offered to account

for it. These theories are based chiefly on laboratory reproductions of shock states. In order to estimate them, I have had to trace the resemblances and differences between experimental shock and shock as it occurs in human cases—a critical procedure made possible by the previous review of facts. Every writer on shock has his own idea as to its nature; I have not broken the tradition, but have summarized the new evidence on the initiating and sustaining factors in the complex, as they have been revealed in the course of recent investigations.

In the last chapters, I have brought together the suggestions which have been made regarding treatment. Again these suggestions have been considered with respect to the experience which medical officers have had on a relatively large scale during the War.

Throughout the presentation of the facts and theories of shock, I have indicated where our knowledge is deficient and where new facts should be sought. The reader should understand from the beginning that the mystery of the onset of shock has not been definitely cleared away despite a considerable increase in our knowledge of it, and that there still remains much work to be done before we shall have elucidated all the factors which play a rôle in its establishment.

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TRAUMATIC SHOCK

CHAPTER I

CHARACTERISTICS AND TYPES OF SHOCK

In the literature of surgical shock, complaint is often expressed that there is no clear definition of the condition. It seems to me that, in such a complex as shock, definition is not a prime requisite. The important matter is to obtain a careful description of the observed facts. Fortunately, we have such descriptions from competent clinical observers. The following is an abbreviation of an account given by Fischer (1):

The patient, a strong and perfectly healthy young man, was struck in the abdomen by the pole of a carriage drawn by runaway horses. We have not been able, after careful examination, to find any trace of injury to any of the internal organs. Nevertheless, the grave symptoms and the alarming look which he still presents made their appearance immediately after the accident. He lies perfectly quiet and pays no attention whatever to events about him. The pupils are dilated and react slowly to light. He stares purposelessly and apathetically straight before him. His skin and such parts of the mucous membranes as are visible are as pale as marble, and his hands and lips have a bluish tinge. Large drops of sweat hang on his forehead and eyebrows, his whole body feels cold to the hand, and a thermometer indicates a degree and a half Centigrade in the axilla and a degree in the rectum, below the normal. Sensibility is much blunted over the whole body, and only when a very painful impression is made on the patient does he fretfully pull a wry face and make a languid defensive movement. If the limbs are lifted and then let go, they immediately fall as if dead. The urine is scanty and dense, but free from any traces of sugar and albumin. The pulse is almost imperceptible and very rapid. The arteries are small and the tension very low. The patient is conscious, but replies slowly and only when repeatedly and importunely questioned. On being thus questioned, he complains of cold, faintness, and deadness of the extremities. His respiration is characterized by long, deep, sighing inspirations, alternat-

ing with very superficial ones, which are scarcely visible or audible. While being brought to the hospital he vomited several times, and nausea and hiccoughs still remain. His pallor, cold skin and hoarse voice immediately recall the appearance of a cholera patient; characteristic dejections are alone wanting to make the resemblance complete.

This description by Fischer accords closely with the account of a typical case as given by Warren (2):

A patient is brought into the hospital with a compound comminuted fracture where the bleeding has been slight. As the litter is gently deposited on the floor he makes no effort to move or look about him. He lies staring at the surgeon with an expression of complete indifference as to his condition. There is no movement of the muscles of the face; the eyes, which are deeply sunken in their sockets, have a weird, uncanny look. The features are pinched and the face shrunken. A cold, clammy sweat exudes from the pores of the skin, which has an appearance of profound anemia. The lips are bloodless and the fingers and nails are blue. The pulse is almost imperceptible; a weak, threadlike stream, may, however, be detected in the radial artery. The thermometer, placed in the rectum, registers 96° or 97° F. The muscles are not paralyzed anywhere, but the patient seems disinclined to make any muscular effort. Even respiratory movements seem for the time to be reduced to a minimum. Occasionally the patient may feebly throw about one of his limbs and give vent to a hoarse, weak groan. There is no insensibility, but he is strangely apathetic, and seems to realize but imperfectly the full meaning of the questions put to him. It is of no use to attempt an operation until appropriate remedies have brought about a reaction. The pulse, however, does not respond; it grows feebler, and finally disappears, and "this momentary pause in the act of death" is soon followed by the grim reality. A post-mortem examination reveals no visible changes in the internal organs.

From symptoms appearing in such cases as these, therefore, we may say that shock is a general bodily state which occurs after severe injury and which is characterized by a persistent reduced arterial pressure, by a rapid thready pulse, by a pallid or grayish or slightly cyanotic appearance of the skin which is cold and moist with sweat, by thirst, by superficial rapid respiration, and commonly by vomiting and restlessness, by a lessened sensibility and often by a somewhat dulled mental state. Such are the easily recognized features of the patient whose injuries have brought him into the shock state. Further examination will reveal a number of other conditions which are likewise characteristic, but for

the present the foregoing descriptions may be regarded as sufficiently typical to identify the complex we are examining.

The Onset of Shock.—It is probable that the term "shock" was originally used to designate a sudden collapse due to a severe wound. There is common employment of the term in this sense, but it is now used for such a wide variety of meanings that a definite significance should be given the word if it is to be used at all. In the sense in which the term is used in this monograph it does not at all imply sudden onset. On the contrary, until further analysis has refined our meaning, it should be understood that the symptoms described in the preceding paragraphs—symptoms which are more or less persistent and which do not lead to immediate death—will be regarded as comprised under the designation "shock," whether they appear suddenly or not.

It has been observed by surgeons and by others who have had opportunity to watch the development of the symptoms of shock that in some instances they appear at once or very soon after the injury and in other instances only after an interval of several hours. Thus, Mitchell, Morehouse and Keen (3), in their report to the Surgeon General of the United States Army in 1864, described cases occurring after wounds of grave nature, in which the patient, immediately after being wounded, suffered from a state of depression which continued and which was marked by great weakness, feeble circulation, pallor, etc. This is immediate shock. The case described above by Fischer is an instance of it.

In other cases, shock is delayed. Especially during the recent World War reports were brought in by stretcher-bearers and regimental and battalion medical officers that, for a considerable period after the reception of severe wounds, patients were to all appearances in good condition and only after several hours did the state of restlessness, anxiety and final depression begin to be evident. Santy (4), as early as October, 1916, wrote a paper in which he called attention to his experience that the severely wounded, before being transported, have a temperature still normal, a pulse which, though rapid, presents a satisfactory tension, and a general state which is not disturbing; in a word, the wounded are not yet shocked. Initial shock, he declares, is much more rare than has been stated. Archibald and McLean (5), in 1917, quoted Santy and declared that from what had been related by British medical officers, serving with battalions and advanced field ambulances, the statements of Santy should be regarded as correct. This testimony was confirmed by Quénu (6) who reported that he had questioned

many of his former students attached to aid posts and that they had informed him that the wounded who were received less than an hour after being hit show a certain amount of restlessness and some anxiety regarding the gravity of their wounds, but with the exception of those suffering from concussion (the *commotionnés*), they are not in a state of shock. Picqué (7) likewise has affirmed that immediate shock is rare; that the wounded arrive at the advanced dressing stations, the second or third hour after being wounded, still warm and in good condition, and that shock is even more rare in the line than in the advanced dressing stations. Finally, Soubeyran (8) has testified that immediate shock, which follows at once on being wounded, is seen only with the *commotionnés*. He himself never saw it, however, and the *commotionnés* whom he was called to observe some hours after they had been injured were far from being in a state of shock. I well remember seeing some wounded men shortly after they had been bombed on a road in the St. Mihiel salient in September, 1918. One of them especially attracted my attention, a man with his right arm torn away by a bomb fragment. His pulse and general appearance at the time were satisfactory. That evening at a mobile hospital, where he arrived after a long journey, he was in profound shock. The general testimony regarding the onset of shock, at least under conditions of warfare, is that it is only rarely present immediately after the reception of the wound and is a state which comes on gradually after the lapse of several hours.

Classification of Shock.—In order to obtain more information regarding the development of shock, the group working at Béthune made arrangements for recording a continuous history of cases from the trenches, where the men were wounded, through the advanced dressing station and back to the casualty clearing station. For this purpose, Capt. E. M. Cowell went to the front lines and there coöperated with regimental medical officers in observations on men as they lived in the trenches, as they were returning from raids, and as they were found shortly after being wounded. Other observations were made by other members of the group as the wounded were carried to the rear for hospital attention. In consequence of tracing and recording the cases in this manner from the beginning and through the early stages of transportation, Cowell has classified shock into two groups—*primary* and *secondary* wound shock.

Primary wound shock is seen when the damage sustained by the body is so great that death must supervene unless surgical intervention is soon available. The blood pressure falls rapidly and all the symptoms

of shock are observed as soon as the patient is seen. It is Cowell's judgment that in war surgery such a state rarely occurs except when associated with hemorrhage. The condition is unavoidable, but in favorable cases may be kept from progressing and may later terminate in recovery. The following case illustrative of primary wound shock has been described by Cowell (9):

On a cold, wet muddy night a man was seriously wounded by a shell while digging a new trench. He was brought to the advanced dressing station 50 minutes later and found to have sustained severe multiple wounds, including compound fractures of femur and humerus. The exposed lacerated muscle looked like dead tissue, there were no vessels of any size bleeding, and hardly any capillary oozing. The blood pressure was 40 mm. Mentally the patient was quite bright and responsive, so that the medical officer in charge of the case remarked how wonderfully fit he was. The man was dead, however, within the hour.

Secondary wound shock is the characteristic type of the phenomenon in the seriously wounded. The symptoms appear only after the lapse of some hours. Early observations reveal no alteration in pulse rate and no lowering of normal blood pressure. In the course of a few hours, however, especially through the action of accessory factors to be considered later, the blood pressure begins to fall, the pulse rate to rise, and the other phenomena of shock likewise to become established. The following case illustrates the development of secondary shock:

A man belonging to the garrison was wounded by a bomb which partly shattered the forepart of his foot and sprinkled his neck and shoulder with tiny fragments. His chum, standing by his side, was killed. The blood pressure, which was 110–70 mm. Hg. a short while previously, was still the same immediately after he was wounded. It was a cold night, with a chilly wind, and as the man was carried along shallow trenches winding over a hill he became colder and colder. At this time, too, there was occasional enemy activity. By the time he reached the aid post, an hour and a half later, he was pulseless. Two hours later, when examined at the next post, he was still pulseless and a serious view was taken of his condition. He was hurried on to the casualty clearing station, where he arrived with a pressure of 80–65 mm. Hg. and no palpable pulse. After being warmed up in bed the pulse soon returned and the shock passed off in the absence of any heroic measures of treatment.

Primary wound shock may be recovered from, at least partially; however, it is likely to develop into the secondary form. In order to make clear the course of events in primary and secondary shock, Cowell (10) has represented in diagrams the blood pressure changes that may be seen in cases of one or other of the two types (see Figs. 1 and 2).

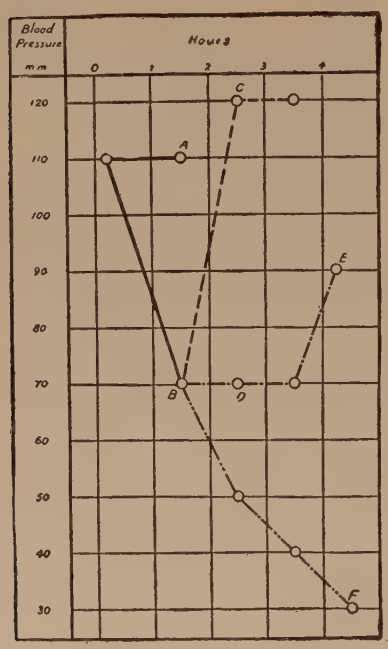

FIG. 1.

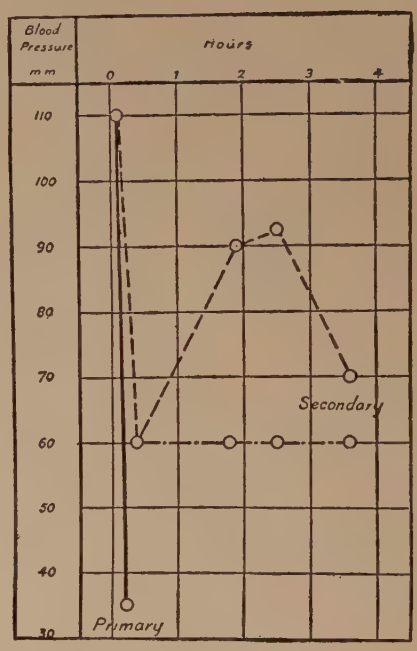

FIG. 2.

FIG. 1.—SECONDARY WOUND SHOCK CURVES (diagrammatic). In many wound cases the pressure will remain level (*A*). In others, as a result of hemorrhage or exposure to cold, there will be a drop of pressure with the establishment of a secondary shock (*B*). If the patient is at this stage well cared for and the wound not too severe, the pressure will rise during the next stage of the journey (*C*) or remain stationary (*D*), improving after admission to the casualty clearing station (*E*). In the absence of favorable circumstances, the pressure goes steadily down and the case terminates fatally, usually in from twelve to twenty-four hours (*F*) (Cowell).

FIG. 2.—PRIMARY WOUND SHOCK CURVES (diagrammatic). Following the receipt of a severe injury, such that death must ensue or life can be saved only by prompt surgical interference, instant shock appears. This may be fatal in a short time. If all precautions are taken in the careful transit of the patient, the pressure may rise en route or remain level without further drop. After the lapse of a few hours the condition of primary wound shock merges into that of secondary wound shock unless recovery has first occurred (Cowell).

French observers have offered similar classifications. Thus, Quénu (6, p. 69) has described what he calls immediate, primary, and secondary shock. The *immediate* onset is associated with disturbances of the nervous system or serious hemorrhage; *primary* may be the result of hemorrhage or toxemia, or of the two coöperating; and *secondary* is

associated with infection, more or less complicated with the factors which have appeared in the preceding stages. Soubeyran (8) likewise separates cases into the three classes mentioned by Quénu, but he subdivides primary shock into hemorrhagic and non-hemorrhagic types. The hemorrhagic cases are those in which there has been an important vascular lesion with much loss of blood, associated also with chilling and exposure and insufficient nourishment; the non-hemorrhagic cases may be only moderately wounded but may suffer from a depression due to cold and exposure. This type, which he regards as of nervous origin, is quite rare. Pure non-hemorrhagic shock is seen only among the severely wounded, that is, in men with multiple wounds, with extensive injury of the limbs, or with severe lesions of the viscera. The phenomena are observed in such cases before the period of infection has arrived, and, furthermore, there is little evidence that any hemorrhage has occurred.

Mouliner (11) has distinguished three varieties of shock according to origin—nervous, hemorrhagic and infectious. There is little doubt that each of these factors plays a rôle in the development of shock, and that one or other frequently predominates in special instances. Possibly these three varieties are roughly related to the temporal groups, the nervous and hemorrhagic fitting into the primary class, and the infectious into the secondary. For the present, however, we need note only these groupings according to etiology.

The foregoing proposals for classification have little significance except in relation to understanding the nature of shock and its treatment. It seems unnecessary now to consider further details of types than those given by Cowell—primary and secondary shock. Thus we may recognize that wounds so serious as almost necessarily to prove mortal, or wounds accompanied by profuse hemorrhage, may be associated immediately or soon with evidences of shock. Along with these severe wounds there may be instances of the complex appearing relatively early in "high-strung" individuals who have not been severely wounded. Cases of this sort were reported to me during the War—one, an officer, who was merely shot through the hand, and another, a man with only a bullet wound in the thigh. Wallace (12) cites two cases in which all the classic symptoms of shock appeared though there had been no gross injury whatever. Primary shock may be seen, therefore, either in the mortally wounded, or after extensive hemorrhage, or in the relatively rare instances in which nervous elements seem to play an important rôle.

On the other hand, after moderately severe wounds, such as complicated compound fracture of the femur or a lacerated wound of muscle with little hemorrhage, there may be no immediate depression. When two or three hours have elapsed, however, the typical indications of shock may begin. This is before infection has developed to a degree that would account for the change. It may be regarded as true secondary shock. Exposure to cold, lack of water, rough carriage and absence of splinting of broken bone have been recognized as circumstances favorable to the onset of the symptoms. A still later aspect of secondary shock is that which is attended by infection, especially with gas bacilli.

Syncope and Collapse in Relation to Shock.—In the foregoing account, emphasis has been laid on the persistence of low blood pressure as typical of shock. In human beings the supply of blood to the cerebral vessels depends on maintaining a head of arterial pressure which is adequate to drive a stream of blood through them while the individual is in the upright position. In other words, the cerebral circulation is dependent on vascular tone throughout the body. Any temporary loss of this tone may result in such increase of capacity of the vascular system that the blood is drawn by gravity into lower channels, and consequently does not flow to the brain. The person then falls in a faint, or suffers syncope, due to the effects of anemia on nerve cells. Such an event may result from sudden bad news; or from a violent stimulus applied to certain regions of the body, as for example, the epigastric region or the testicle; or it may occur when persons who have long been in bed attempt to assume the erect position. It is characteristic of syncope, however, that the individual, on lying down or having the feet raised or the abdomen compressed, regains consciousness and does not suffer subsequently. Cowell (13) reports observations on three soldiers who fainted shortly after being wounded. The blood pressure, which was taken as soon as possible after the recovery from the faint, was found to be normal. It seems possible, however, that in some cases, such as were reported by Mitchell, Morehouse and Keen, there may be persistent "reflex paralysis" of the blood vessels or their nervous control, and a shocklike state thus induced. There is general testimony, however, from officers who served in the World War, that such cases are rare.

The symptoms of shock and collapse are practically identical. Collapse has been described as a sudden great fall in blood pressure, such as may be seen after severe hemorrhage or after continuous loss of circulating fluid, as in cholera, or after vasomotor paralysis arising from violent afferent impulses. There is nothing in such descriptions which

differs in any way from primary shock, and it seems possible, therefore, that the two conditions may be regarded as indistinguishable.

In accordance with the foregoing classification, the problem of accounting for shock resolves itself into discovering the course of events in the nervous or hemorrhagic primary manifestations, and in the retarded or delayed manifestations which have been most commonly observed. In the discussion which follows, the observed facts will be considered in detail before attempts are made at giving explanations.

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CHAPTER II

THE LOW BLOOD PRESSURE

Earlier observers noted that patients suffering from shock had a thready, easily compressible pulse. The devising of methods for measuring arterial pressure in man has permitted a fairly accurate estimate of the systolic pressure, and of the diastolic pressure as well, in persons suffering from this condition. The inferences drawn by earlier observers have thus been confirmed in more exact terms. There is no doubt that a highly characteristic feature is a lowered arterial pressure, indeed this low pressure is probably the central feature, or one of the most essential features, of shock. A number of the other phenomena, such as the disturbances due to slow circulation, the thirst, and the rapid superficial respiration, promptly disappear when the arterial pressure is raised by transfusion of blood or the infusion of an indifferent solution. Furthermore, the degree of reduction of pressure may be regarded as a fairly satisfactory index of the degree of shock which is prevailing. And finally, if the pressure continues to fall, the prospects of the patient are properly regarded as becoming more and more unfavorable, whereas if the pressure begins to rise and continues rising toward a normal level, the prospects of the patient are properly regarded as improving. There is no more important aspect of the complex of established shock than the state of the circulation as indicated by the sphygmomanometer.

Limitations of Blood Pressure Criteria.—Although a diminished arterial pressure may measure the degree of shock, and the course of the pressure changes may indicate the tendencies in the patient, there is strong probability that, in the development of the condition, especially in cases of secondary shock, a stage is passed through in which the arterial pressure, though maintained at a normal level, is accompanied by such a serious disturbance of the blood flow as to render the individual's chances precarious. This stage, as will be seen later (see p. 49), appears in the production of shock under laboratory conditions and can be demonstrated readily after severe hemorrhage. Thus, as illustrated in Fig. 3, there may be repeated hemorrhage of considerable amount—20 per cent

at the first bleeding (2:29), and 10 per cent at the second (2:48), in this instance—with a restoration of nearly the original arterial pressure. In some examinations of venous blood soon after the recovery of pressure in such cases, Major H. O. Robertson found no notable reduction of the hemoglobin percentage. The blood volume clearly had not been made up, during the short period of recovery, by inflow of fluid from the tissues, for that would have diluted the blood and reduced the hemoglobin reading. The restoration of pressure may be accounted for as the result of such constriction of arteries, and probably of capillaries and

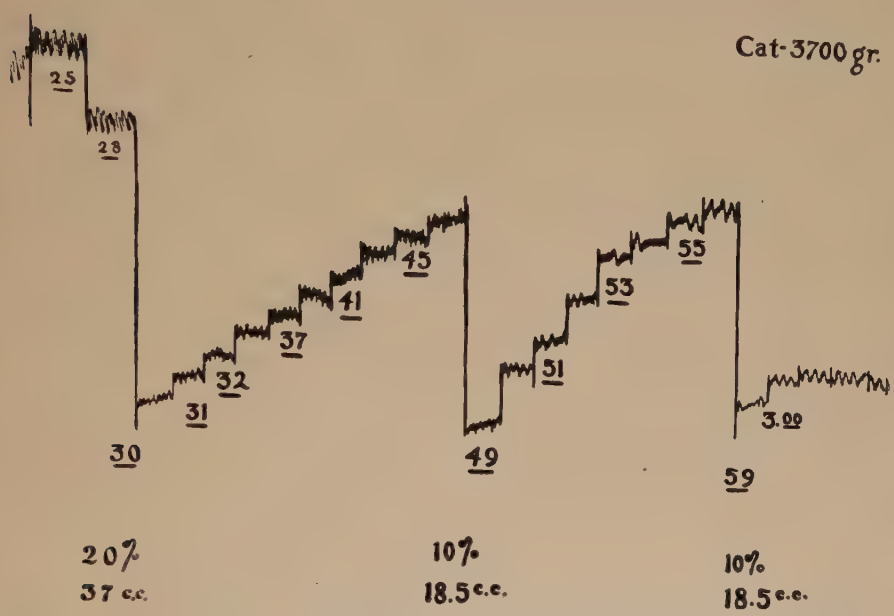

FIG. 3.—RECORD SHOWING PROMPT RECOVERY OF BLOOD PRESSURE AFTER HEMORRHAGE. (Twenty per cent of the estimated blood volume at 2:29, and 10 per cent at 2:48.) Failure of recovery after a critical further bleeding (10 per cent) at 2:58.

venules as well (9), that the capacity of the circulatory apparatus is reduced to correspond with the reduced volume. Under these circumstances, though the record of arterial pressure is satisfactory, the organism is obviously not in the same condition as before: and further experiment proves that the removal of an amount of blood which normally would be without effect will break the compensation and immediately produce a permanently reduced pressure (see Fig. 3, third bleeding, 2:58). This may be called the "critical further bleeding."

The clinical evidence that a similar stage is passed through in the development of shock lies in the fact that several of the characteristic

features of the condition, such as pallor and sweating, may be prominent and may lead the observer from superficial appearances to make a diagnosis of shock, though the pressure proves to be not markedly reduced. Action unfavorable to the patient may then quickly change the status so that the pressure falls promptly to a typical shock level.

J. H. C., Canadian, was brought into No. 33 C. C. S., Béthune, with a shell wound and compound fracture of the right upper arm. He seemed in fairly satisfactory condition. The blood pressure was 102 systolic, and 80 diastolic. Though the operation involved simply a quick removal of the arm, the pressure fell promptly, and at the close was recorded as 50–28.

The determination of arterial pressure in shock is often difficult. I have seen cases in which the pulse was not palpable at the wrist and in which it was impossible to hear with the stethoscope the characteristic clear systolic sound at the elbow, as compression of the upper arm was released; nevertheless the pulse could be felt in the neck. Even when the point of systolic pressure can be definitely fixed, the determination of diastolic pressure may be very difficult; there may be no distinct muffling of the sound as the compression of the arm is gradually lessened, and the sound may continue without much alteration until it gradually disappears at a point which is hard to define. The figures for diastolic pressure, therefore, though desirable for the calculation of pulse pressure, should not be regarded in the records of the pressure readings of shock cases as possessing the accuracy of the figures representing systolic pressure.

The Range of Arterial Blood Pressure in Shock.—In a series of 93 cases of shock and hemorrhage, about half of them examined at Béthune (1) and the others reported to the English Shock Committee by Bazett (2) and by Keith (3), the distribution of the *systolic* pressures were as follows:

41–50	mm.	mercury	6	cases
51–60	"	"	14	"
61–70	"	"	17	"
71–80	"	"	26	"
81–90	"	"	16	"
91–98	"	"	14	"

The average systolic pressure in this series was 76 mm. of mercury.

The *diastolic* pressures in these cases, so far as they could be ascertained, were distributed as follows:

21–30 mm. mercury	.....	8 cases
31–40 " "	.....	23 "
41–50 " "	.....	24 "
51–60 " "	.....	30 "
61–70 " "	.....	8 "

The average diastolic pressure in this series was 48 mm. of mercury. The average pulse pressure—the difference between systolic and diastolic pressures—in the cases under examination was 28 mm. of mercury. In general this proves to be higher for the higher systolic pressures than for the lower. Thus, if the records are classified in groups according to systolic pressures as above (91–98, 81–90, etc.), and the average figures for each group are calculated, the results are as follows:

Average Systolic Pressure	Corresponding Average Diastolic Pressure	Average Pulse Pressure
95	63	32
87	57	30
76	49	27
66	41	25
58	36	22
47	30	17

The systolic pressure in normal young men varies between 110 and 120, and the diastolic between 65 and 75 mm. of mercury. The pulse pressure, therefore, may vary between 35 and 55 mm. Evidently shock is associated not only with reduced systolic and diastolic pressure but especially with a reduced pulse pressure.

Brechot and Claret (4) have reported that the pulse pressure is of prognostic value. If it remains above 25 mm., according to them, the prognosis is favorable; at 25 mm. it is questionable; and below 25 mm. the prospects are wholly dark. In cases which I have seen, the presence of other significant elements than pulse pressure was so common that I am unable to bring support to their claim.

The Blood-Pressure Index of Shock.—In 1916, McKesson (5) laid down a rule, sometimes referred to as "McKesson's rule," which was intended to indicate the incidence of shock in the course of a surgical operation. He pointed out that normally, with a diastolic pressure of 80 mm. of mercury and a pulse pressure of 40, the ratio of diastolic pressure to pulse pressure is as two to one. In shock both these pressures decrease and often in such a way, according to McKesson, as to make the pulse pressure less than half the diastolic pressure. "When the pulse pressure," he states, "has reached 20 mm. or less and is associated with a diastolic pressure of less than 80 in a patient who at the beginning of the operation had presented normal pressures, frank shock has occurred." As the figures given in the foregoing tables indicate, a state of shock, as judged by clinical observation, may be present long before the pulse pressure is likely to be nearly so low as 20 mm. Furthermore, in every instance in the rather large number of cases recorded above, the average pulse pressure was more than half the average diastolic pressure. It seems, therefore, that the suggestion that there must be an altered ratio between pulse pressure and the diastolic pressure in order that the state of shock may be regarded as imminent or existent, is misleading. For the present we may regard a systolic pressure which remains persistently below 100 mm. and a diastolic below 65 mm. in a wounded man as indicative of danger. Such pressures should, indeed, be associated with other signs of the shock state. Evidence will be presented later to show that, when the systolic pressure falls and remains below 80 mm., serious effects may occur which will add to other factors operating to augment or to prolong shock. In judging a patient's condition it will always be necessary to regard, so far as possible, the total complex presented by him rather than a single feature such as McKesson's rule implies.

The Venous Pressure in Shock.—Although plans had been made for securing observations on venous pressure in shock cases, the ending of the War before these plans could be realized, rendered them futile. Information regarding venous pressure has important bearings on certain theoretical suggestions as to the nature of shock, as we shall see, and it is unfortunate that definite data were not obtained. In drawing blood for tests, however, I have had occasion to introduce a needle into veins in scores of instances. If venous pressure were high in shock this procedure would have been easy because the veins would have been prominent. In fact, however, they were rarely found prominent, and often there was much difficulty in making them so by compressing the arm

gently with a soft rubber tourniquet. It required special skill to puncture these collapsed or contracted vessels through the skin and sometimes they had to be exposed in order that the blood sample might be obtained.

In this connection the observation of Morison and Hooker (6), that in shock produced experimentally by intestinal injury the pressure in the vena cava progressively fell, and Wiggers' (7) testimony that shock as induced by him, that is, by prolonged afferent stimulation, was accompanied by a lessening of effective venous pressure, coincide with the clinical observations just recorded. Erlanger, Gesell and Gasser (8) likewise noted that in shock following intestinal manipulation, jugular pressure did not increase but varied below the original level.

The Factors Affecting Blood Pressure.—One of the central problems, if not the most important central problem, of shock is that of discovering the reason for the lowered arterial pressure. The various theories which have been suggested to account for shock are all directed towards the solution of this problem. In order that we may get as much insight as possible into the underlying elements of the disturbance we shall turn our attention first to the factors which are concerned in the maintenance of normal pressure.

Normal arterial pressure may be reduced if the heart becomes inefficient, that is, if it contracts ineffectively or feebly. There is, consequently, a possible cardiac factor.

Again, arterial pressure may be low because of diminution of peripheral resistance. Normally the arterioles are held in a state of tonic contraction by impulses delivered from the vasomotor center. If the vasomotor center becomes impaired there will be such a relaxation of the smooth muscle in the walls of the arterioles as to permit the blood to pass readily from the arterial into the capillary and venous areas with an attendant drop in the pressure level. A second possible factor, therefore, is a diminution or loss of vasomotor tone.

A third factor which would result in low pressure is an insufficient blood volume. As illustrated in Fig. 3, the blood vessels, up to a certain limit, are capable of compensating by contraction for a loss of blood volume. When this limit has been reached, however, any further diminution of blood volume must occur within the minimal capacity of the vessels. It follows that there is not enough volume to fill these channels, and necessarily the pressure within them diminishes. Another way in which the relation between the volume of the blood and the capacity of the vessels may become disturbed is through enlargement of the capacity of the vascular system, particularly of one portion, such as the

veins, for example. The blood may then accumulate there and consequently be returned in so slight a stream as not to permit the heart to develop a normal pressure within the arteries. The disturbance of the normal relation of volume of circulating fluid to the capacity of the circulatory apparatus presents, therefore, another mode by which the circulation may become defective or fail.

In the following chapters, I propose to consider the clinical and experimental evidence regarding the part played by each of the three factors just mentioned in producing the conditions which prevail in shock.

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CHAPTER III

THE QUESTION OF VASOMOTOR EXHAUSTION IN SHOCK

In their report to the Surgeon General in 1864, on cases of sudden collapse following wounds, Mitchell, Morehouse and Keen (1) called the phenomenon which they described, "reflex paralysis." The theory which they offered was that shock "either destroys directly the vital power of a nerve center, or it causes paralysis of the vasomotor nerves of the center." The suggestion that the state of low blood pressure in shock is due to weakening or exhaustion of the nervous mechanism, whose function it is to keep the arterioles in a state of tonic contraction, has had earnest advocates and is still commonly accepted.

The Evidence for and against Vasomotor Exhaustion.—The best known support for the view that shock is due to vasomotor exhaustion has come from the experiments of Crile (2). After ruling out the heart as a causal factor in shock he looked to the loss of peripheral resistance as the essential factor. This might be due either to exhaustion of muscles in the vessel walls or to exhaustion of the vasomotor center. Since adrenalin caused as great a rise of pressure in shock as it did in normal conditions, and since adrenalin produces its effect by stimulating directly the muscle of the arterioles, Crile concluded that fatigue of the blood vessels themselves must be excluded. As, in his reasoning, the one other factor involved in causing low blood pressure was the vasomotor center (he seems not to have regarded reduction of blood volume), he concluded that shock is due to an exhaustion or breakdown of this center. Later, in 1905, Mummery (3) supported Crile's view that the steady fall in general blood pressure which occurs in shock results from exhaustion or fatigue of the vasomotor center.

In further work Crile (4) extended his view that shock is due to vasomotor exhaustion so that the concept was gradually developed that shock consists essentially of exhaustion of cells in the brain, the liver and the adrenal glands.

A lowering of arterial pressure is obviously not proof that the vasomotor center is inactive or exhausted, for arterial pressure may be low in consequence of hemorrhage, a state in which a reduced volume of

blood is delivered to the heart for each contraction. Furthermore, Porter (5) and his collaborators (6) found that, even when an animal is in extreme shock, both pressor and depressor reflexes still occur. The presence of depressor effects proves that some tonic activity of the vasomotor center is still present, for otherwise its action could not be depressed; and the pressor reflexes show that the center is still capable of increased action when stimulated. The results observed by Porter were independently confirmed by Seelig and Lyon (7) and also by Mann (8). Mann further tested the effect of asphyxia in shock and observed a marked asphyxial rise of blood pressure—a rise which is known to be the result of vasomotor stimulation.

The Condition of the Vasomotor Center in Shock.—Since the vasomotor center is not primarily exhausted, the question arises as to its actual condition in shock. Recent experimental evidence leads to the conclusion that in shock there is a tonic nervous control of both peripheral and visceral arterioles. Seelig and Lyon (9) found that cutting an important nerve of the leg in a shocked animal caused an increased flow of blood from the femoral vein, a result to be expected if the arterioles had previously been held in tonic contraction, for they would then relax on being denervated and would permit a larger stream to flow through them. Guthrie (10) in confirming this work observed that whereas the increase of flow in a normal animal was 22 per cent, in a shocked animal it was as much as 76 per cent. Later, Seelig and Joseph (11) noted that if in a shocked rabbit with the vessels of one ear denervated, the blood pressure was suddenly raised by clamping the aorta, the blood greatly distended the arteries of that ear but failed to distend the arteries of the other ear whose nerves were still connected with the vasomotor center. The denervated blood vessels, therefore, relaxed passively in the presence of increasing internal pressure, whereas the ear vessels which were normally innervated were well constricted. This phenomenon was demonstrated while the animal was sinking into the condition of shock and also after shock had developed. Seelig and Joseph found that this vascular constriction persisted even when the blood pressure was raised close to the normal level; the constricted state of the arterioles, therefore, was not merely effective in the presence of a low pressure. That the constriction was certainly due to vasomotor impulses was proved by cutting the sympathetic fibers or by abolishing their conductivity with ether or by freezing; thereupon constriction of the vessels promptly disappeared. Similar observations were made by Mann (12) and by Morison and Hooker (13) on internal organs. A

number of other investigators have reported that, in animals with low blood pressure, the rate of perfusion flow is less with a given pressure of the perfusion fluid than it is in a normal animal, and that severance of the nerves to the organ or increase of the blood flow to the vasomotor center increases the rate. The observation of Muns (14) that during the onset of shock in dogs, the hind leg, as measured by plethysmograph, is diminished in volume, is additional testimony that the blood vessels in shock are contracted.

Studies by Pike, Guthrie and Stewart (15) have revealed, moreover, that the vasomotor center is more capable of withstanding the adverse influence of anemia than any other of the vital bulbar centers—those of the respiratory, the cardio-inhibitory or the swallowing mechanisms. Its capacity to function is the last to disappear in consequence of total anemia and the first to reappear when the blood flow is restored. Obviously the vasomotor center should be regarded as an agent whose functions are extremely stable and whose capability of continued service is its most outstanding feature. And, in endangering circumstances, such as lessened blood supply, it becomes, for a time at least, more than usually active.

The recent experimental studies of shock have brought out the distinction between the state of the vasomotor center in early and in late stages of shock. Erlanger, Gesell and Gasser (16), using a method described by Bartlett (17) determined *directly* the variations in peripheral resistance as shock progressed. Salt solution was made to flow from time to time under constant pressure through the femoral artery of one hind leg. The inflow cannula was always placed in a side branch of the artery so that when injections were not being made the branch could be excluded and the leg thus permitted to receive its natural blood supply. These investigators produced shock by intestinal exposure and manipulation, as well as by temporary partial obstruction of the aorta (18), and noted in both conditions that the rate of perfusion of the salt solution was at first unimpaired or actually decreased. This maintained peripheral resistance, thus directly demonstrated, clearly indicates that in the early stages of shock vasomotor tone is still normal if not augmented. Later, as the pressure falls, the peripheral resistance begins to diminish and by the time the pressure has reached the vicinity of 50 mm. of mercury (in cases of abdominal shock), the peripheral resistance is practically invariably below normal. Up to the time of death, however, the vessels preserve some tone and the vasomotor center some slight capacity to react.

The observations above cited are supported by studies made by Cattell in the Harvard Physiological Laboratory on shock produced by muscle injury. The method employed to test vascular tone was that used by Erlanger and his collaborators. The results are presented in Table I.

TABLE I

TIME REQUIRED FOR 1 C.C. OF SALT SOLUTION UNDER CONSTANT PRESSURE TO FLOW INTO PERIPHERAL VESSELS

Exp.	Control Time for Inflow Sec.	Maximal Time for Inflow Sec.	Time After Muscle Injury Hrs.	Per Cent Increase of Time	Time for Inflow at End Sec.	Time for Inflow after Death Sec.	Original Blood Pressure mm. Hg.	Blood Pressure at Maximal Constriction mm. Hg.
VIII	5.2	12.9	3 to 4	144	4.7	1.8	140	90
IX	2.3	3.3	1	43	2.9	1.2	130	16
X	1.4	2.4	4	71	....	.8	140	74
XII	1.2	2.7	4½	125	1.1	.5	130	68
XIV	.8	1.5	1½	87	1.0	1.3	130	60
XV	1.3	3.7	1¼	185	....	....	120	72
XVI	1.6	4.0	3½	150	....	....	135	78
XVIII	2.7	4.0	4½	48	....	....	125	65
XIX	1.5	2.5	6	66	....	1.1	135	42
XX	1.4	2.5	..	78	....	....	130	92
XXI	1.0	1.7	3	70	.9	.6	130	60
Av. . .	1.85	3.74	3	102	2.1	1.0	131	65

The figures in the first, second, fifth, and sixth columns give the time in seconds for the passage of 1 c.c. of fluid into the vessels and represent the averages of at least three determinations. Invariably, there is a gradual decrease in the rate of inflow (that is, increase of time for 1 c.c. to pass) after the muscle injury, usually starting within the first hour and reaching a maximum in from two to four hours. At this time of maximal constriction, the blood pressure had already fallen to shock level, the average pressure for the series of experiments being 65 mm. of mercury. Following this stage a dilation occurs, with a faster perfusion rate which continues until death and is accompanied by a further fall in blood pressure. After death the perfusion rate is still further in-

creased, showing, as in Erlanger's experiments, a further dilation. A graph displaying the general relations between the blood pressure and peripheral resistance in Cattell's experiments is given in Fig. 4. It represents the averages of six experiments which were carried out over a period of four hours or more.

Evidence for Maintained Vasomotor Tone in Human Cases.—Advocates of the view that shock results from vasomotor exhaustion

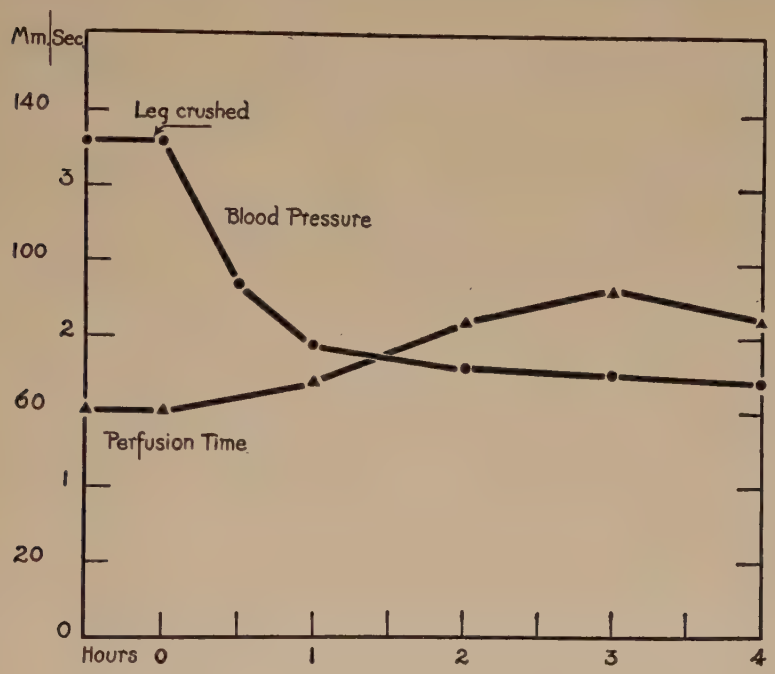

FIG. 4.—CURVE PLOTTED FROM THE AVERAGES OF SIX EXPERIMENTS. This curve shows the relationship between the perfusion rate and the blood pressure in muscle-injury shock. As the blood pressure falls, there is a slowing of the perfusion rate, indicating an increased tone of the arterioles.

have assumed that, in the large splanchnic vessels especially, the blood would be gathered if vascular tone were lost. As long ago as 1909, however, Malcolm (19) declared that every surgeon knows that splanchnic congestion is "never observed in the state of profound shock induced by an unusually severe or prolonged abdominal operation. On the contrary, the more profound the degree of shock the paler the tissues become, and the pallor of the tissues and of the peritoneum is noted even when very little blood is lost." This testimony is supported by Wallace, Fraser and Drummond (20), surgeons with extensive ex-

perience at casualty clearing stations during the World War, who performed many hundreds of abdominal operations on patients in all stages and degrees of wound shock. They have recorded the fact that on opening the abdomen in such cases they have not found any primary splanchnic congestion.[1]

At Béthune we observed not infrequently in shock cases that when the pulse could not be felt at the wrist, it could be felt easily if the palpating fingers were moved to the arm where the arteries were larger, or were applied over the carotid. And Fraser repeatedly noted, while operating on shocked men, such strong contraction of outlying arteries that no bleeding occurred when the vessels were cut.

Recently Ducastaing (21) has reported that in two cases of shock, when the pulse was weak or wholly imperceptible, the wave became quite readily palpable under the action of amyl nitrite. Because of the well-known vasodilator effects of this drug, Ducastaing has argued that the results which he observed are further evidence that in shock peripheral vessels are constricted.

Reduction of Vasomotor Activity from Reflex Stimulation and Concussion.—Although the foregoing discussion has revealed that commonly in traumatic shock there is no primary exhaustion of the vasomotor center, the fact that cases have been reported similar to those cited by Mitchell, Morehouse and Keen, to which the name primary shock has been given (see p. 7), indicates that there may be in certain individuals, and under certain circumstances, a more or less lasting depression of the vasomotor center, due to severe wounds.

The experimental proof that there may be a reflex inhibition of vascular tone started with observations by Goltz (22), who in 1863–1864 found that repeated blows on the viscera in the frog caused a temporary cessation of cardiac contraction and paralysis of vascular tone. This was accompanied by a gathering of blood in the vessels to such a degree that the heart, on starting to beat again, was at first small and pale because of failure of the blood to return to it. A similar condition will prevail on cutting the splanchnic nerves and releasing the

[1] Late in April, 1917, I was invited to give the Shattuck Lecture before the Massachusetts Medical Society. On May 6, I was ordered into military service. The authorities despaired of finding another lecturer at short notice. To accomodate them, I prepared the lecture before leaving for France on May 11. It was entitled "Physiological Factors in Surgical Shock" (Boston Medical and Surgical Journal, 1917, clxxvi, 859). It showed the effects of hasty composition. One of the central assumptions in the argument was that the blood was stagnant in the large abdominal veins—an idea soon destroyed by experience at Béthune.

great splanchnic area from tonic control of the vasomotor center. It has been assumed, therefore, that Goltz's observation and conclusion regarding reflex vasomotor paralysis would account wholly for the conditions which obtain in shock.

In his observations on wounded men in frontline positions, Cowell (23) had occasion to note in a number of instances that slight wounds were followed by a temporary fall of blood pressure which resulted in fainting. It is possible that this phenomenon might be more persistent in certain cases than in others. It happens, however, that in our experience we observed no instance of severe shock which followed promptly in a reflex manner from slight wounds. Fischer (24) reports, however, the case of a powerful man who was bitten in the testicle by an angry horse and who, a few hours after the injury, died in deep shock.

Besides a reflex fall of blood pressure, there may be a fall due to the effects on the vasomotor center of cerebral concussion. In experiments performed by Porter and Storey (25) a blow on the skull caused the blood pressure to fall 70 per cent. In five observations the level reached by the descending pressure averaged 33 mm. of mercury. It is well known that concussion will inhibit the function of nerve cells and sometimes lead to more or less permanent functional disturbances.

There is a question here, as in our earlier discussion of the classes of shock, whether the above occasions for the fall of blood pressure are really to be regarded as in the same category with the cases in which there has been extensive injury of limbs or viscera. The temporary fainting which may be seen after wounds is possibly in the nature of syncope rather than shock. It should be understood, however, that there are instances, probably rare, such as the one cited above by Fischer, in which a persistent low blood pressure may be induced, with death supervening, though the initial wound involved relatively little tissue destruction.

The conclusion to be drawn from the evidence presented above, is that, ordinarily, in shock, exhaustion of the vasomotor center, or even weakening of its tonic activity, is not *primarily* the cause of the low blood pressure. As we shall see later, however, if the blood pressure is allowed to remain low for some time, the bulbar centers, together with the heart and other organs, may have an insufficient supply of blood. Damage is certain to result if this condition persists, and in consequence there will be relaxation of vasomotor tone..

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CHAPTER IV

THE QUESTION OF A CARDIAC FACTOR

As has been often observed, the heart characteristically beats faster than normally in shock and after hemorrhage. In 84 cases of this character, which were included in the 93 cases reported in Chapter II, the average pulse rates ranged between 123 and 133 per minute, as shown in the following figures:

Number of Cases	Systolic Pressure	Average Pulse	Range
12	51–60	133	114–160
16	61–70	133	100–160
26	71–80	126	104–144
16	81–90	126	96–160
14	91–98	123	108–140
84			

It will be observed that in no instance was the rate lower than 96 and that in three cases it was as high as 160. I myself have rarely seen the heart beating faster than 144 per minute. It seems possible that this is a limiting rate for continued action under the circumstances. The average rates as shown above are invariably lower than this. It is noteworthy that the average pulse varies relatively little as compared with the variations in systolic pressure.

The Suggestion That the Vagus Center Is Exhausted.—In the course of experimental work in which operations on the brain were performed, Howell (1) noted that there was produced a marked increase in the pulse rate—for example, changes from 66 to 120, 87 to 162, 70 to 171 beats per minute. Since this extraordinary increase of rate was observed in cases which might exhibit only slight lowering of arterial pressure, Howell felt that a distinction between cardiac and vascular shock was justified, and he assumed

that in cardiac shock the most important factor is a partial or total suspension of activity of the vagus or cardio-inhibitory center. The condition manifested itself in his experiments as a sudden or progressive increase of rate and diminution of amplitude of the heart beat. What Howell calls vascular shock—namely, a more or less complete loss of arterial tone—he never observed independent of cardiac shock; the latter always accompanied or preceded the fall of pressure.

The suggestions offered by Howell have been tested by both Crile and Mann. In 1903, Crile (2) reported having obtained reflex inhibition of the heart in animals which had been reduced by trauma to a degree of shock presumably fatal. Furthermore, he declared that shock is as readily produced in animals in which the heart is isolated from the central nervous system, as it is in animals with that connection intact. Mann (3) likewise found that shock did not develop any more quickly under experimental conditions when the vagi had been cut than when these nerves were intact. He also noted that reflex inhibition of the heart by stimulation of the central end of a divided vagus trunk could be obtained even in the most extreme degrees of shock. Again, the well-known vagus slowing of the heart after a large injection of adrenalin, as well as after an increase in intracranial pressure, still occurred in shocked animals; and the effects disappeared after section of the vagi. These experiments seem to prove conclusively that in traumatic shock the cardiac inhibitory mechanism is not exhausted and that it may be called into action by usual means.

In experiments performed to obtain information regarding some conditions of activity of endocrine glands, Smith and I have observed that the heart may be greatly augmented, even as much as 80 beats per minute, by removal of the cerebral cortex, even though all cardiac nerves have previously been severed. Furthermore, opening the abdominal cavity, and even slight manipulation of the intestine, will sharply increase the rate of the denervated heart. It appears, therefore, that, under experimental conditions, there are agencies at work—in the cases mentioned, probably the adrenal glands, and possibly the liver—which may increase the cardiac rate without involving the action or inhibition of nerve centers.

The Suggestion That the Heart Is Tonically Contracted.—Boise (4) has reported experiments in which he has registered, by a myocardiograph, the variations of cardiac contraction during shock.

His records show a diminution of the extent of contraction, associated with a lowered arterial pressure. This phenomenon he interprets as being due to tonic contraction of cardiac muscle—"a cardiac spasm."

The cardiac volume necessarily diminishes with a diminished return of blood to the heart; and in consequence of a diminished output from the heart, arterial pressure falls unless the vasoconstrictor center is capable of compensating adequately for the lessened discharge into the arteries. The phenomena registered by Boise, therefore, can readily be accounted for as secondary to vascular or volume changes. It is not necessary to regard the heart as a primary factor in them. Indeed Henderson (5), who likewise has registered a decrease of cardiac volume, that is, "cardiac tetanus," in shock, states that it is probably a secondary phenomenon and that the apparent cardiac failure is the result of diminution of the pressure and volume of the venous stream to the right heart.

Further evidence that increased cardiac tonus, or "cardiac spasm," such as would lead to diminished cardiac output, is not the primary cause of shock, is found in the state of venous pressure. Clearly, venous pressure would rise if the heart were suffering from a diminished capacity to transfer blood from the venous to the arterial side. Both clinical and experimental evidence has indicated that venous pressure does not rise and may indeed fall as the arterial pressure falls during the development of shock (see p. 14). There is no evidence, therefore, that a tonic contraction of the heart in shock is a primary occasion for the low arterial pressure.

The Suggestion That the Contractile Power of the Heart Is Impaired.—Impairment of the inherent contractility of cardiac muscle results in an insufficient transfer of blood from the venous to the arterial side of the circulation. Such impairment, according to Wiggers (6), is the cause of circulatory failure after nitrites and is frequently the cause of death in cardiac disease.

Henderson (7) has argued that cardiac failure may occur in consequence of excessive respiration. He has applied vigorous artificial respiration to an animal, lasting thirty minutes. Thereafter apnea occurred and continued until, from lack of oxygen, the heart failed, eight minutes later. The inactivity of the respiratory center is ascribable to depletion of the body's store of carbon dioxid. This condition of *acapnia*, that is, reduced carbon dioxid in the blood, Henderson believes may occur to such a degree, after intensely painful

stimulation, as to lead to failure of respiration and consequently to damage of the heart muscle and thus possibly to death. In support of his view, Henderson cites three instances in which death occurred as a result of total cessation of breathing after a period of excessive respiration which had resulted during stimulation of the sciatic nerve. This fatal *apnea vera* was associated with a heart beat which became progressively weaker until it finally ceased. In recent experiments, Wiggers (8) has produced by sciatic stimulation greatly increased depth and rate of respiration, but in no instance, even after nearly two hours of stimulation, did permanent apnea or death from respiratory failure occur, as Henderson had reported.

Whether Henderson or Wiggers is correct regarding the effects to be expected from excessive respiration, it is clear that the acute weakening of cardiac contraction and the sudden cessation of the heart beat in consequence of lack of oxygen do not duplicate the events which take place actually in the course of shock. The wound which a man receives may be accompanied by pain, and he may later be subjected to a degree of pain which might evoke unusually deep and rapid breathing; but any one who has seen many cases knows that the approach of death from shock is not attended by the conditions which Henderson produced in his experiments. To be sure, respiration ceases commonly before the final heart beats, but cessation of respiration is not preceded by intense hyperpnea due to painful stimulation. It cannot be considered correct, therefore, that failure of cardiac contraction, in consequence of an apnea due to excessive breathing, is the cause of death.

Evidence as to the Condition of the Heart in Shock.—As a result of extensive study of shocked animals, Mann (3) has reported that, when they are allowed to die from shock itself, the heart still beats, though sometimes feebly, after respiration has ceased and the blood pressure is practically at zero. I have repeatedly observed the same sequence of events at death in cases of shock in human beings.

On the basis of their observations on the isolated heart, Marckwalder and Starling (9) advise that systolic blood pressure be maintained at 90 mm. of mercury at least, in order to avoid an insufficient supply of blood to the contracting mechanism. If, after a period of low blood pressure, which may have weakened the cardiac muscle, the pressure is raised and the flow through the coronary arteries is increased, the heart may quickly recover its capacity to do its normal work. In a series of experiments, Crile (2) observed that after animals had been reduced to a degree of shock presumably fatal

and the blood pressure was then raised much higher than normal, the heart nevertheless performed its proper function. Mann (3) likewise has reported that he has given large doses of adrenalin to shocked animals after vagus section and has thus increased arterial pressure to a level six times as high as that which had previously prevailed; in every instance in which this was done the heart was able to pump effectively against the very high pressure and in no instance was there indication of cardiac failure. Similar tests made by raising arterial pressure by increase of intracranial tension likewise proved that the heart, when adequately supplied with blood through increased coronary flow, is competent to perform its functions.

During the period in which resuscitation classes were taught in the Surgical Research Laboratory of the A. E. F. at Dijon, it was customary each week to produce shock in an animal and, after the low blood pressure had continued for several hours, to kill the animal by asphyxia. Two or three minutes after the blood pressure had been dropped to zero and there were no oscillations in the record ascribable to ventricular contraction, warm normal salt solution containing adrenalin was run into the carotid artery, artificial respiration was begun, and the heart was massaged through the chest, in the manner described by Crile (10). Uniformly there was a restoration of the heart beat. Almost immediately the blood pressure rose to 150 or even to 180 mm. of mercury. In only one instance, out of about twenty-five trials, was there any sign that the heart was in difficulty in the presence of this large load suddenly applied to it, even though it had suffered a long period of shock and extreme asphyxiation.

The testimony of clinical experience accords with that given by laboratory experiments. During the last year of the War, the common method of treating shock consisted in transfusion of blood or intravenous injection of salt solutions. I was in a position to hear of unfavorable results which might arise from applying these measures. Even when there was no permanent rise of blood pressure as a consequence of increasing the volume of circulatory fluid, there was regularly a primary rise. In only one instance have I heard of an immediate death (a case of blood transfusion). This might have been due to too rapid increase of volume, so that the right heart was overwhelmed.

The foregoing review has revealed no convincing evidence that

either the heart muscle itself, or the nervous agencies controlling the heart, exhibit any changes in shock which justify the conclusion that they are primary factors in lowering arterial pressure. The heart may indeed be injured, as may other organs, from a prolonged inadequate supply of blood, and when thus ill treated it may ultimately fail. Both clinical and experimental evidence, however, show that, when properly nourished, cardiac muscle is readily capable of carrying on its normal task.

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CHAPTER V

SHOCK AS DUE TO DISCREPANCY BETWEEN BLOOD VOLUME AND VASCULAR CAPACITY

The evidence adduced in the two previous chapters shows that at first, in most cases of shock, the vasomotor center is efficiently at work and the heart is capable of assuming any reasonable burden which may be placed upon it. Physiological analysis has indicated that the only other factor which might lead to a persistent low arterial pressure, is such reduction in the amount of blood returned to the heart that the cardiac output becomes insufficient to sustain the normal level.

The essential condition, when the circulation fails through an inadequate return of venous blood to the heart, is a discrepancy between the volume of circulating fluid and the capacity of the circulatory system. There may be, on the one hand, too great a capacity. Since this is not primarily due, in most cases of shock, to a relaxation of arteries and arterioles, it has been assumed that the difficulty lies in the veins—that there is a derangement of some venopressor mechanism. On the other hand, the discrepancy may arise from a reduced blood volume, that is, the volume of the blood may be less than enough to fill the vessels even when they are most contracted. There are advocates of each of these views and their evidence should be presented.

The Evidence For and Against Venous Atony.—Henderson (1) has declared that injury to spinal or bulbar nerve centers has no direct effect upon the venopressor mechanism. The evidence for his conclusion is that: (*a*) after section of the vagus nerves, vigorous stimulation of the splanchnic nerve causes a rise of arterial pressure but a barely perceptible effect upon pressure in systemic veins; (*b*) after vagus section, adrenalin raises arterial pressure with an insignificant effect upon venous pressure unless cardiac contraction is disturbed; (*c*) section of the cervical spinal cord causes a marked fall of arterial pressure, but no important drop in venous pressure; (*d*) stimulation of the severed cord under curare restores arterial pressure but causes no rise, or only

a temporary slight rise, of venous pressure. On the other hand, according to Henderson, if carbon dioxid is allowed to accumulate in the body, as in intratracheal insufflation, arterial pressure continues unaltered, but a rise of venous pressure develops; and if carbon dioxid, in addition to oxygen, is allowed to flow into the trachea, the rise of venous pressure develops in a few minutes. If artificial respiration is now performed the venous pressure falls again. This series of experiments, Henderson believes, clearly demonstrates that there is a venopressor mechanism and that the control of it is largely chemical—dependent upon a proper tension of carbon dioxid in the blood and tissues. "This phenomenon of hyperacapnial (that is, excess carbon dioxid) venous hypertension affords a convincing demonstration of the existence of the venopressor mechanism. It appears to be a crucial experiment for this mechanism very much as section and stimulation of the cervical sympathetic nerve in the rabbit were crucial for the recognition of the vasomotor nervous mechanism."

Earlier than this Bayliss (2) had reported that carbon dioxid, when added to Ringer's solution which is perfused through the limb vessels of frogs, causes vascular *relaxation.* This observation has been repeatedly confirmed by Hooker (3) who found that in minimal effective amounts carbon dioxid always relaxes vascular muscle. Further, Hooker (4, p. 598) observed a rise of venous pressure on stimulation of the nerve to a part, for example, a leg, or by stimulation of a sensory nerve which evoked a reflex rise, or by central stimulation through asphyxia; in other words, Hooker's experiments support the view that venous tone is under nervous control and that increase of carbon dioxid diminishes instead of increasing peripheral venoconstriction.

In a later paper, Henderson and Harvey (5, p. 541) have declared that Hooker has misunderstood the previous argument. They make a distinction between "venopressor" and "venoconstrictor" effects. They conceive that venous pressure would be increased by relaxation of the venules, "allowing readier outflow from the tissue reservoirs," and that constriction of the venules by damming the blood back in the capillaries would decrease the venous return to the heart. It seems to me that Henderson has little evidence that the venules are in fact constricted in shock, or that they, by constriction or relaxation, are capable of exercising such control as to influence profoundly the circulation. The expressions "tissue reservoirs" and "damming the blood in the capillaries" have apparently been used without considering the lack of evidence of any large accumulation of blood in capillary areas.

To summarize, then, there is a conflict of evidence regarding the central nervous control of venous tone, with the positive evidence in favor of such a control. Later views of Henderson (5) appear to coincide with those of his critics, namely, that increase of carbon dioxid relaxes vessel walls. Henderson (5, p. 541) now explains the increased venous pressure, observed when the carbon dioxid content of the blood is increased, by a relaxation of venules which he assumes were previously constricted, and which, in relaxing, allow pent blood to escape from hypothetical tissue reservoirs. It seems more reasonable to account for the increased venous pressure, seen when the carbon dioxid tension rises in the blood, in terms of actual venoconstriction due to increased nervous stimulation, in accordance with Hooker's evidence. From this review we may conclude that the chemical venopressor mechanism probably plays a relatively slight rôle in controlling the circulation.

It is probable that prolonged low pressure, which is associated with loss of constrictor tone in the arterioles, would also be associated with loss of constrictor tone in the veins. I am not acquainted with any direct evidence on this point, though Hooker (4, p. 594) reports that the nerve centers which control venous tone are likely to lose their functional power under the conditions of experimental procedure.

The Evidence for Reduced Blood Volume.—If the discrepancy between the volume of circulating fluid and the capacity of the circulatory system is not primarily due to dilation of the veins or the capillaries, there remains the possibility that it may be due to actual reduction of the quantity of the blood itself. The important question, as to whether there is in shock cases a reduction of total blood and plasma volume, was answered by a study of a series of cases of wound shock conducted by Keith (6). The method employed, which was devised by Keith, Rowntree and Geraghty (7), consisted essentially of introducing into the blood stream a known amount of vital red, a non-toxic, non-diffusible dye, and later comparing the color of the plasma with a known standard.

In performing the test 6 to 8 c.c. of blood are first removed from an elbow vein and then, without removal of the needle, a known quantity of the vital red solution is slowly injected. The first blood sample is gently shaken in the withdrawal syringe and poured into a paraffined tube. After three to five minutes, the time allowed for admixture of the dye with the circulating blood, a second speci-

men of blood is withdrawn, 8 to 10 c.c., and emptied into two paraffined tubes. From one of these second samples blood is taken into a hematocrit tube. The hematocrit and paraffined tubes (tightly corked) are then centrifuged at high speed for 20 minutes and the plasma pipetted off. In order to make the test, a standard solution is prepared by diluting 0.5 c.c. of the original dye solution to 100 c.c. with 0.8 per cent of NaCl solution. The two solutions for comparison are made up as follows:

Standard { 1 part of the diluted dye solution
1 part of the plasma before dye injection
2 parts 0.8 per cent NaCl solution

Test { 1 part of plasma after dye injection
3 parts 0.8 per cent NaCl solution

One c.c. was taken for convenience as 1 part. The two solutions are then compared in a Duboscq colorimeter and the test or unknown solution read off in percentage against the standard.

The following formula is used for calculating the plasma volume:

$$\frac{200}{R} \times \text{No. of c.c. dye injected} \times 100 = \text{c.c. plasma.}$$

R = per cent reading of test solution.

The blood volume is calculated from the hematocrit reading—100 : per cent plasma : : x : c.c. plasma.

Hemolysis must be avoided, for when it takes place, a brownish tint is given to the test solution of plasma, which makes the colorimeter reading difficult.

Robertson and Bock (8) have suggested a method of determining blood volume by estimation of the drop in percentage hemoglobin produced by intravenous injection of a known amount of Bayliss's gum-salt solution (6 per cent gum acacia in 0.9 per cent sodium chlorid). The method is illustrated in the following case: The patient had a hemoglobin percentage of 61.5. After injection of 580 c.c. of the acacia solution, the hemoglobin fell to 52.5 per cent, a drop of 14.6 per cent of the original 61.5. With the addition of a colorless diluent to a colored fluid the intensity of color should be lessened in inverse ratio to the increased volume of the solution. Taking 61.5 as 100, therefore, the formula for estimating the new volume would be

$$100 : 14.6 : : x : 580$$

$$14.6 : : 58{,}000 \quad \text{or} \quad x = 3{,}973 \text{ c.c.}$$

Subtracting 580 from 3,973 gives the volume before the gum injection. Estimations made with vital red at the same time in this case showed a volume of 3,844 c.c. The error is approximately 3 per cent.

In the series of cases studied by Keith each patient was weighed before the test was made, and values for total blood volume and plasma volume were compared with those of normal men of the same weight. Total blood volumes were found to be constantly reduced in soldiers suffering from wound shock. Further, the diminished blood volume was recognized as bearing a definite relation to the severity of the patient's clinical state. In twenty-seven of the twenty-nine cases of wound shock, which formed the basis of Keith's study, the estimated blood volumes ranged from 52 to 85 per cent of the normal, and there was a corresponding reduction of plasma which ranged from 62 to 90 per cent. In the remaining two cases, the hemoglobin percentage and clinical symptoms indicated marked reduction of blood volume but direct determination was not made.

In normal individuals, the withdrawal of a considerable quantity of blood, even as much as 800 c.c., is followed by a fairly prompt return of the original volume, due, no doubt, to passage of fluid from tissue spaces into the blood stream. In shock, however, this compensation fails to occur, or occurs to an insufficient degree. A case cited by Keith brings out this fact especially well. In this instance, about twenty-four hours after 600 c.c. of gum acacia solution had been injected intravenously, the percentage hemoglobin was 125, indicating a marked concentration of the blood. Severe symptoms of wound shock were present and the patient died. At autopsy, no definite external wounds were found and no gross internal hemorrhage had occurred. Some factor appeared to be at work which permitted the escape of plasma from the vessels.

On the basis of clinical observation and the degree of reduction of blood volume, Keith (9) found that cases of wound shock fell into three groups, as follows:

Group I—*Compensated Cases.*—In this type the patient's general condition is good. He has no distressing symptoms except the local pain of the wound and a feeling of general weakness. He is often very pale, and may have suffered moderate bleeding after receiving the wound. The pulse is increased to 90 or 110, the systolic blood pressure

remains above 100 mm. Hg., and the blood volume is never reduced below 80 per cent of the normal. This amount of reduction of blood volume seems to be the maximum decrease that occurred in this series without giving rise to marked untoward symptoms. The plasma volume does not show a proportionate reduction; it is 85 to 90 per cent of normal, thus giving evidence that dilution, though delayed, is taking place spontaneously.

Group II—*Partially Compensated Cases.*—Here the patient's general condition is not good. There is usually a history of a smart hemorrhage. The patient is pale, restless, thirsty, and vomits readily. The extremities are cold and partially anesthetic to painful stimuli. The pulse rate is rapid, 120 to 140, and difficult to count; the systolic blood pressure is, as a rule, below 90, usually 70 to 80 mm. Hg. The blood volume ranges between 65 and 75 per cent, and dilution has occurred slowly, the plasma volume ranging from 70 to 80 per cent.

Group III—*Uncompensated Cases.*—These patients are in an extremely serious condition. They are as a rule restless, very thirsty, and vomit immediately on being given fluids. The extremities are cold to the touch. The pulse cannot be readily felt, the arterial blood pressure may be as low as 60 mm. Hg. On auscultation the heart rate is found to be 120 to 160. Certain of these cases have a heart rate below 100, but this is almost invariably a terminal phenomenon. The blood volume is below 65 per cent. The lowest plasma volume obtained was 62 per cent, so that dilution was remarkably retarded.

The relations between low blood pressure and reduced blood volume given by Keith correspond roughly with earlier estimates made by Robertson and Bock (8). They expressed the opinion, after studying a smaller group of cases than that comprised in Keith's series, that with a blood pressure below 95 mm. Hg. the blood volume is under 70 per cent, and that, with the pressure 80 mm. or less, the volume is 60 per cent or under.

Reduction of Blood Volume in Experimental Shock.—In their experimental studies on wound shock, Gasser, Erlanger and Meek (10) induced the condition by injecting large doses of adrenalin or by clamping the aorta or vena cava, or by manipulating the intestines. They estimated the blood volume by use of the method devised by Meek and Gasser (11), according to which the intravenous injection of a known amount of gum-saline solution is followed by a determination of the dilution undergone by the acacia in the

blood, after time for mixing has been allowed. In all forms of experimental shock observed by Gasser, Erlanger and Meek, the blood volume was found to be decreased. This was not a phenomenon of severe shock alone but began to appear soon after starting the procedure employed to produce shock.

In some instances, typical shock was found in animals whose absolute blood volumes were decreased merely from 7 to 17 per cent of the normal. The only explanation for the existence of shock in these cases, as given by the observers, is that there was an enlargement of the vascular bed, that is, an increased capacity, and therefore greatly reduced effective volume. Gesell (12) has shown, however, that a decrease from 8 to 18 per cent of the normal blood volume is of itself significant. He found that a loss of blood by hemorrhage of less than 10 per cent of the estimated blood volume may elicit by vasoconstriction a decrease of flow (for example, through the submaxillary gland) of more than 60 per cent.

Relation of Shock to Hemorrhage.—As illustrated in the case cited above by Keith, there may be shock, with reduction of blood volume, and without indications of hemorrhage. Experimental shock is typically of this character; it is produced by internal changes of blood volume and not by actual loss of blood from the body. The fact is clear, however, that, with severe wounds, hemorrhage into injured tissues or externally from ruptured vessels, so that there is a real and permanent loss of blood, would be an additive factor in developing the shock state. An analysis which leads to the conclusion that shock is due to a diminished volume of circulating fluid obviously places the phenomena of shock and of hemorrhage on similar planes. The dictum uttered by the older generation of surgeons, that "shock is hemorrhage and hemorrhage is shock," thus receives a striking confirmation.

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CHAPTER VI

THE PROBLEM OF THE "LOST BLOOD"

As pointed out in the foregoing chapter, evidence of reduced blood volume has been found in both clinical and experimental shock, without any indication of external hemorrhage. This observed fact raises a question which is one of the most difficult in the entire mystery of shock—where in the body is the blood which is out of currency? There are no indications that it is in the heart or lungs; it must be, therefore, in systemic arteries or capillaries or veins.

Is It in the Arteries?—That the lost blood is not in the arteries is sufficiently proved by facts already discussed. With an efficient vasomotor center and a capable heart, an adequate amount of blood in the arteries would be accompanied by satisfactory arterial pressure. Just because the pressure is low under such circumstances is evidence, as previously stated, that the heart is not supplied with enough blood to fill the arterial system.

Is It in the Veins?—The view commonly held in the past has been that in shock blood is stagnant in the large venous reservoirs of the chest and abdomen and especially in the capacious splanchnic area. In shock, it is said, the "sufferer bleeds into his own abdominal veins." This view appears to have been based largely on experimental evidence which has been rather uncritically accepted. For many years the most certain way to produce shock in a lower animal was by exposure and manipulation of the intestines. The mesenteric veins then stand out prominently, blood gathers in the intestinal walls, and the structures that have been freely handled appear as if inflamed (1, 2). In other words, blood obviously stagnates in abdominal vessels. Such a condition is not actually seen in shock in human beings. The testimony of surgeons who have had extensive experience at advanced hospitals in the recent War, and who have performed many abdominal operations on patients suffering from wound shock, has already been mentioned—they testify

that on opening the abdomen they have not found any evidence of splanchnic congestion (3). The method previously employed to produce shock in lower animals, which has repeatedly called attention to the abdomen and its peculiar circulation, seems to have given rise to misleading inferences as to what occurs in natural shock brought on by wounding other than the abdominal region.

The failure to observe the collection of blood in the abdominal veins would not be due to difficulty in perceiving it there. According to Keith (4), the venous cistern in man, formed by the big veins of the chest and abdomen, has a capacity of about 450 c.c. Mann (2, p. 439) has observed that the amount of blood obtained by bleeding and by emptying the heart of normal animals is 76 per cent, leaving 24 per cent "in the tissues." When animals are shocked by exposure of the intestines, the amount left in the tissues rises to 61 per cent, a difference of 37 per cent. Similar results have been noted by Gasser, Erlanger and Meek (5, p. 44). If the blood mass of a man of 70 kilos is taken as 5,400 c.c. the amount thus lost would be 2,000 c.c. If this blood were added to that naturally present in the veins of the abdomen, systemic or splanchnic, it is clear that their capacity would have to be greatly enlarged and their distention, therefore, would be easily noted.

If the lost blood, on the other hand, were in the systemic veins, it would be possible promptly to remedy the condition of a shocked individual by placing his body in a slanting, head-down position, bandaging the limbs, and compressing the abdomen. Such measures have been thoroughly tried in treating shock (6) and though perhaps helpful in some cases, they do not give results which indicate that the blood which is out of circulation is stagnant in the large venous channels.

The evidence that veins are subjected to vasoconstrictor impulses has already been mentioned. Venoconstrictor nerves have not been demonstrated for all parts of the body, however, and if there are veins free from nervous control, influences other than nervous might cause relaxation. Only slight relaxation, perhaps too little to be conspicuous, would be needed in veins all over the body to increase considerably the venous capacity, but there is no evidence that the veins are even slightly dilated in shock.

Is It in the Capillaries?—If the lost blood is not in the arteries, and probably not in great amount in the veins, its hiding place should naturally be sought in the capillaries. As pointed out by Gasser,

Erlanger and Meek (5, p. 52) there are several ways in which the effective volume of the blood may conceivably be reduced. The actual blood volume may fall because of (*a*) transudation of plasma, (*b*) jamming of corpuscles in capillaries and venules, or these two processes combined with (*c*) absolute stasis of blood in some part of the vascular system, or (*d*) hemorrhage into tissues or through external surfaces, as into the lumen of the intestines.

Evidence that these processes actually occur is found in the results of recent studies.

Blood Concentration in the Capillaries.—In studies (7) made on shock cases by the group at Béthune, the first typical characteristic of the blood which was noted was a high capillary red count. Of a series

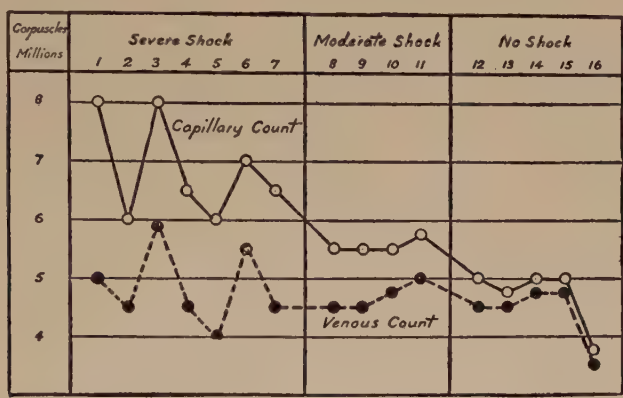

FIG. 5.—COMPARISON OF RED COUNTS, CAPILLARY AND VENOUS, IN CASES OF SEVERE AND MODERATE SHOCK, AND IN PATIENTS WITHOUT SHOCK.

of 27 cases classified as severe traumatic shock, all but 11 had a capillary count which amounted to 6,000,000 corpuscles or higher, and in 8 cases it was more than 7,000,000 corpuscles. When hemorrhage as a complicating factor is considered, tending to reduce the blood count, these high records are striking and indicate that in shock a concentration of the blood, at least in superficial capillaries, is a typical occurrence.

Whether or not the concentration found in capillary blood is true of all the blood, was determined by counting capillary and venous samples taken simultaneously. This procedure revealed a more or less marked discrepancy between the two counts. The capillary samples were taken from widely separated parts of the body—from the lobe of an ear, from a finger and from a toe; the venous samples from an arm vein. In Fig. 5 are plotted observations on 7 cases of severe shock,

4 cases of moderate shock, and 5 cases in which no shock was present. The strikingly higher capillary count as compared with the venous count in the severe cases, amounting approximately to 2,000,000 corpuscles, was reduced in the moderate cases, but even in these the difference was still nearly 1,000,000 corpuscles per cubic millimeter. Control observations made by us on normal individuals did not reveal greater differences than 3 per cent between capillary and venous counts, and comparative samples of capillary and venous blood, drawn before rising from bed in the morning, proved that the discrepancy was not due merely to inactivity. From these considerations it seems evident that the difference between capillary and venous red counts varies roughly with the degree of shock, and, since the venous count is approximately at the normal level or below it, the difference is due to concentration of the blood or stagnation of corpuscles in the capillaries.

When the capillary stagnation has become established it may not promptly disappear. I have seen a patient who had recovered from severe shock so far as arterial blood-pressure readings indicated, but whose hands, from wrists to finger tips, in spite of being warmed, were still bluish gray with stagnant blood.

Hematocrit determinations of the volume per cent of corpuscles, as well as hemoglobin determinations of capillary and venous samples, confirmed observations made by counting. In the case cited in the foregoing paragraph, for example, the hemoglobin reading for the blood in the still abnormal fingers was 114 per cent, whereas that of the blood in the capillaries of the ear, in which a normal circulation had been restored, was 104 per cent. It is clear that blood samples taken from skin areas in shock cases may yield counts or hemoglobin or hematocrit readings which as a basis for judging the deficiency of blood are wholly misleading.

A comparison of some of the blood counts and hematocrit and hemoglobin determinations in our cases is presented in Table II.

As mentioned before, shock is frequently complicated by hemorrhage. In these conditions the capillary red count may be low, but when compared with the venous red count the discrepancy between the two at once appears. In other words, when hemorrhage complicates shock, the blood in the peripheral capillaries contains relatively more corpuscles in a given volume than that in the veins, though in both the number is reduced. Our observations of the concentration of the blood in peripheral capillaries have been confirmed by Taylor (8) and also by Robertson and Bock (9).

TABLE II

VENOUS AND CAPILLARY RED COUNTS, WITH HEMATOCRIT AND HEMOGLOBIN READINGS, IN SOME CASES OF LOW BLOOD PRESSURE

Initials*	Blood Pressure		Red Counts (in millions)		Hematocrit		Hemoglobin	
	Diastolic	Systolic	Venous	Capillary	Venous	Capillary	Venous	Capillary
P. K.	34	52	3.8	5.6	...	...	...	...
A. S.	38	62	4.5	6.4	30	41	...	...
E. G.	40	64	6.2	8.5	30	47	88	113
F. H.	(near	death)	4.0	6.0	31	43	...	...
D. H.	48	64	4.2	5.5	37	41	80	95
S. D.	48	72	4.7	5.3	30	35	75	84
W. W. T.	†	50	5.3	6.4	...	...	92	98
W. C.	58	76	4.5	5.5	...	...	...	...
S. F. S.	58	80	4.9	5.3	...	...	...	...
T. R.	70	92	5.2	5.6	39	44	107	111
J. H. C.	80	102	5.8	6.9	41	45	95	105

*Further information about some of these patients may be obtained by finding these initials in Table I, Cannon: Acidosis in Cases of Shock, Hemorrhage and Gas Infection.
†Irregular.

Experimental evidence that blood may become concentrated was brought forward as early as 1893 by Sherrington and Copeman (10), who called attention to the fact that intraperitoneal operations on animals raised the specific gravity of the blood. Later Cobbett (11) and Vale (12) reported a concentration of the blood in conditions which induce shock. In 1905 Malcolm (13) argued that the blood during shock is subjected to such pressure that the plasma is forced out of the vessels into the tissues; and in 1910 Henderson (14) suggested that in shock, the physicochemical conditions controlling the passage of fluid to and fro through the walls of the capillaries are upset, with the result that the distribution of water in blood, lymph, and cytoplasm is so altered that there is an excessive passage of liquid from the blood into the tissues. In 1915 Mann (2) advocated the same idea, declaring that in shock there is a loss of circulatory fluid at a point beyond vasomotor control; and in a *Memorandum on Surgical Shock,* issued by the English Medical Research Committee (15) in February, 1917, the idea was generalized that various shocklike states, due either to trauma or toxemia, are characterized by a concentration of the blood. In the

human cases studied at Béthune, the concentration which was observed was in superficial capillaries. Unfortunately we did not have, at that time, the suggestion offered by the discovery of Gasser, Erlanger and Meek (5, p. 43) that in experimental shock, produced in various ways, the most constant finding is a corpuscular injection of the intestinal mucosa. They noted that in severe cases the whole of the small intestine was engorged with blood so that it had a deep reddish appearance; microscopically the corpuscles were almost entirely within the vessels except at the injured tips of the villi; the capillaries and swollen veins were greatly dilated and tightly packed with red blood cells and the spleen was usually swollen and had dark areas of hemorrhage. It would be interesting to observe whether, in cases of human shock, there is a concentration in intestinal capillaries as well as in the superficial capillaries of the skin.

The Transudation of Plasma.—The concentration of blood is commonly accounted for by assuming that there is a passage of fluid from the vessels into the tissues. Since the normal mode of interchange is chiefly by passage of water and salts back and forth through capillary walls, it has been supposed that such a transfer occurs in shock. The careful studies made by Gasser, Erlanger and Meek (5, p. 46), however, have shown that in shock produced by clamping the aorta, the protein content of the plasma undergoes no marked change during the process of concentration of the blood. This indicates that the reduced volume of the blood is due to an escape of plasma as a whole. The observation precludes the possibility which has been suggested (14, p. 174) that the fluid is lost from the blood because of an increased affinity of the tissues for water.

In the normal individual after hemorrhage, there soon occurs a dilution of the blood due to the passage of fluid from tissue spaces into the blood stream. The mechanism of this occurrence is explained by Starling (16) as due to such reduction of the blood pressure in the capillaries that the filtration pressure from within them no longer offsets the greater osmotic pressure of the plasma as compared with the lymph, and consequently water passes into the blood stream. It is one of the unexplained features of shock that with the low venous and arterial pressures this process does not occur. Instead, the plasma as a whole makes its escape through the vessel walls.

Though in both shock and severe hemorrhage, blood volume is

reduced, the processes occurring in the capillary region in the early stages of the two conditions are probably exactly opposed; in shock fluid passes outward through capillary walls, reducing the plasma percentage and concentrating the corpuscles; in hemorrhage fluid passes inward to the blood stream, compensating for the lost plasma and reducing the concentration of corpuscles. It has been suggested by Bainbridge and Bullen (17) that a determination of the hemoglobin percentages in cases of severe injury would show whether the patient was suffering preëminently from hemorrhage or shock. It is not known, however, that pathological processes in the capillaries are uniform throughout the body. In shock, for example, capillary permeability is perhaps increased only in certain areas; the low pressure resulting from escape of plasma would then be the occasion for a compensatory passage of fluid into the blood stream through uninjured capillaries in other areas. Under these conditions, the hemoglobin percentage might not alter at all, though active interchange is going on between blood and tissue fluids.

The Increased Viscosity of the Blood.—The viscosity of the blood is complex, consisting, as it does, of the internal friction of the plasma, the friction of the corpuscles with the plasma and with each other, and the frictional contacts of the corpuscles with the vessel walls, especially in the capillaries. A prime factor affecting the viscosity of the blood has been found to be the number of corpuscles per unit volume. In a case of polycythemia with tumor of the spleen (having from 8 to 10 million erythrocytes per cubic mm.), Bence (18) observed that the viscosity of the blood rose from a normal of about 5 to over 20. Cohnheim (19) ascribed the low blood pressure in cholera to a failure of blood to return to the heart, owing to the enormous increase of frictional resistance that is caused by concentration. In cholera, however, as in shock, there is a great loss of fluid from the circulation; but apparently the concentration of the corpuscles in the capillaries would in itself render the friction greater and increase the resistance of an onward movement. According to Trevan (20), the internal friction rises rapidly as soon as the corpuscles reach a certain concentration (60 per cent); they then become contiguous and have a tendency to stagnate, especially when the arterial pressure is decreased. Such stagnation, in addition to hemorrhage and escape of plasma, would further augment the amount of blood which is out of currency, and consequently conduce to failure of the circulation.

Another way in which the viscosity factor might become prominent is through concentration of the corpuscles due to slowness of the blood flow itself. In 1888 Cohnstein and Zuntz (21) noted that when blood pressure is lowered, for example, by cutting the spinal cord, a capillary stagnation occurs to such an extent as to pack the vessels closely, while the venous blood quickly falls in corpuscular content (a drop of about a million corpuscles per cubic millimeter in 10 minutes). Lowering of blood pressure, therefore, may induce a stasis which can be clearly observed in both surface and internal capillaries. A similar phenomenon has been described by Mall and Welch (22). When the blood pressure was lowered in a mesenteric artery by partial or complete occlusion, they saw the smaller and larger microscopic veins become more and more distended with red corpuscles which accumulated in clumps or in solid columns. This jamming of the vessels then extended to the capillaries. After a time, red corpuscles began to pass through the capillary walls, and finally the hemorrhage became so great that a view of the vessels themselves was difficult. This process starts when the arterial pressure is reduced to about one-fourth or one-fifth of normal.

The observations just mentioned point to the possibility that, because of concentration of the corpuscles, due either to transudation of plasma or to slowing of the circulation from a diminished arterial pressure, the small veins and capillaries, certainly in the intestinal wall and perhaps elsewhere in the body, may become more or less permanently plugged with corpuscles. A vicious circle would thus be started in which there would be less return of blood to the heart and consequently a lessened output into the arteries; following on that, a diminished pressure with a slower flow; and a further accumulation of corpuscles, therefore, in venules and capillaries. As pointed out by Gasser, Erlanger and Meek (5, p. 48), the plugging of the capillaries at their distal ends may lead to such increase of capillary pressure as to result in increased transudation of plasma. Thus the action of the factors in the vicious circle might become augmented continuously until complete failure of the circulation would result.

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CHAPTER VII

THE REDUCED VOLUME-FLOW OF BLOOD

The low blood pressure in both experimental and clinical shock is explained by a diminution of blood volume, an actual decrease in the amount of fluid which is circulating. In the early stages of secondary shock, however, the diminished volume may not be associated with a reduced arterial pressure. The only way in which the pressure can be maintained in the presence of a smaller amount of circulating fluid is by a lessening of the capacity of the circulatory system. This diminished capacity, as already noted, is the consequence of extra activity of the vasoconstrictor center, causing greater contraction of peripheral vessels. When the blood pressure begins to fall there may be also passive contraction of these vessels because they are no longer distended by the internal pressure which normally prevails. With further development of shock there is a fall of arterial pressure below the limits of normal variation, a fall which is accounted for by reduction of the blood volume below the minimal capacity of the system and by a final relaxation of vascular tone as the vasomotor system becomes less active.

The effects of the changes above outlined are fundamentally important to an understanding of the sequence of events in shock. In order to comprehend their significance, it is necessary to refer to the primary principles of the circulation. We must keep in mind the fact that the blood circulates in order to supply with food and oxygen the tissues which are remote from the alimentary tract and the lungs, and to carry waste from these tissues to surfaces where it may be excreted. The interchange between the flowing stream and the active tissues occurs in the *capillary* portion of the circulatory system. This is the essential region. All other parts of the circulation —heart, arteries and veins—exist in order to provide a continuous flow of blood through the capillaries. The high head of pressure normally maintained in the arteries serves, first, to keep a constant flow passing through the capillaries in all parts of the body, no matter what extra

demands are placed upon the general supply of blood by organs which, becoming active, have dilated vessels. Secondly, this high head of pressure assures speed in the passage of blood from the heart back to the heart again. And since the function of the blood as a common carrier depends on the number of trips which it makes from places where it is loaded to where it is unloaded, the speed of the circulation is evidently an important determinant of the capacity of the blood for service in the body.

The Effects of Decreased Blood Volume.—With a decreased volume of blood the blood pressure may still remain at its normal level (see Fig. 3). One might suppose from the restored blood pressure that the blood supply to all parts of the organism is occurring at its normal rate. The admirable investigations of Gesell (1) have shown, however, that this is far from being the case. The vasoconstriction which takes place when, in consequence of hemorrhage or tissue injury, the blood volume is reduced, is not uniform throughout the vascular distribution. Gesell's observations prove that under such circumstances the volume-flow through the submaxillary gland, for example, is greatly diminished. In one instance, a removal of 10 per cent of the estimated blood volume of the animal caused a reduction of the volume-flow per minute through this gland amounting to 60 per cent of the basal flow, that is, the amount passing through the gland when at rest. This occurred even though there was no fall of arterial pressure. The volume-flow is obviously of the utmost importance in the delivery of oxygen to the tissues, for each red blood corpuscle is a carrier. If the number of carriers is reduced to this great degree, as a consequence of slight hemorrhage or slight reduction of blood volume, it is obvious that the tissues are in danger of an insufficient supply.

It should not be supposed that all parts of the body are affected in the same way as the submaxillary gland when vasoconstriction compensates for diminished volume. There is good evidence (2) that in the presence of normal arterial pressure the blood vessels of the central nervous system and the heart do not undergo contraction. The effect, therefore, of a peripheral constriction which would shut down the volume-flow of peripheral structures, would serve to maintain an adequate volume-flow in the essential organs.

The Effects of Decreased Arterial Pressure.—Gesell's studies prove that the volume-flow to peripheral organs is more diminished by reduction of blood volume than by reduction of blood pressure.

When blood pressure begins to fall, however, the force which is driving the blood through the capillaries begins to become less effective, consequently the rate of flow will, as a rule, steadily diminish as the pressure falls. Thus the volume-flow not only to peripheral structures but also to the essential organs, such as the central nervous system and the heart, will become gradually less and less.

Diminished blood volume, therefore, results in a lessened blood supply to peripheral tissues because of a primary vasoconstriction; and lessened blood pressure results in diminished blood supply both to peripheral tissues and to central organs because of a slower flow. All parts of the body may then begin to suffer from disturbances of the circulation, initiated by diminished volume of blood and continued as the volume becomes less and less.

The Importance of a Sustained Blood Flow to the Brain.—The materials delivered to the tissues by the flowing blood may be classified into food, water and oxygen. The degree of dependence of cells on these materials varies with the materials and also with different groups of cells. Thus there may be prolonged absence of fresh food supply in the blood without disturbance of function. A less prolonged absence of fresh water supply in the circulating stream is also endured without serious damage. The need for oxygen, however, is quite different from the need for either food or water. It is urgently necessary that oxygen be continuously delivered if tissues are to keep active.

Of all the cells in the body the neurons appear to be most sensitive to lack of oxygen; and among neurons there are some types which are much more sensitive than others. For example, total anemia of the brain for 8 minutes will induce in certain cells of the cerebral cortex (the small pyramidal cells) such profound changes that there is a permanent loss of function (3). The bulbar nerve centers are less sensitive than the cortical, for they may manifest renewed activity after being deprived of their oxygen supply for 20 or 30 minutes. Nerve cells of the cord and of sympathetic ganglia have been found still capable of activity after an anemia of approximately one hour; and Burket and I (4) showed that the nerves of the myenteric plexus were not permanently damaged by anemia lasting approximately three hours.

If, on the basis of present evidence, we grade tissues in accordance with their resistance to want of oxygen, it is clear that there is less capacity to resist, that is, greater liability of injury, in the cen-

tral nervous system than elsewhere in the body, and that in this system the functions of the brain are more likely to be disturbed than those of other parts. The evidence presented above has shown that as blood volume diminishes, the volume-flow decreases until the amount supplied to different parts of the body may be greatly reduced. In the less sensitive structures of the periphery, the reduction, according to Gesell's observations, may be as low as 35 per cent of the amount supplied when the organ is at rest. No exact determination has been made of the reduction of the volume-flow to the central nervous system as the blood pressure falls. The only data bearing upon the question, of which I am aware, were obtained by Howell (5) in an examination of the effects of perfusing the cerebral vessels with defibrinated blood or a mixture of defibrinated blood and Ringer's solution, under varying pressures. He was interested in the effects of subnormal and supernormal pressures, and most of his experiments involved such high levels in the arteries as to be beyond the normal range. In one case, however, he reports the effect on the blood flow through the brain of a change of pressure from 30 to 122 mm. Hg. With 30 mm. Hg. the outflow was 5.26 c.c. per minute. When the pressure was raised to 122 mm. Hg. the outflow was 34.52 c.c. per minute. In other words, when the pressure was increased fourfold, the outflow was increased nearly sevenfold. A reduction of the pressure from 122 to 30 mm. Hg. was followed by a reduction of the outflow to 2.22 c.c. per minute, that is, about one sixteenth of the rate at the higher level. Although these experiments must be regarded as having been done under abnormal conditions, they are clearly indicative of the direct dependence of the rate of flow on the height of arterial pressure, and they suggest that as the pressure falls the rate of flow falls to a much greater degree.

From the foregoing considerations it is probable that, as the volume-flow to the tissues becomes more and more reduced in consequence of diminished blood volume and lower arterial pressure, the transportation of the most urgently needed material, that is, oxygen, is greatly decreased in amount. It becomes a matter of importance, therefore, to learn whether there actually is an insufficient oxygen supply delivered to the tissues when the flow of blood through the capillaries is much reduced.

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CHAPTER VIII

THE REDUCTION OF THE ALKALI RESERVE

In 1910 Henderson (1) pointed out that, in the absence of an adequate supply of oxygen, the development of acid substances in the tissues might be expected, in consequence of the partial asphyxia. Later, Crile (2) and his co-workers reported results which indicated that a condition of "acidosis" is present in various clinical states, including shock. And in 1917, during a study of the toxemia of gas-gangrene, Wright (3) observed a reduction of the alkalinity of the blood serum as determined by titration with acid to a certain end point. Patients suffering from gas-gangrene have many of the symptoms of shock, and Wright argued that the "acidemia," as he called it, of this condition was the cause of these symptoms.

During the summer of 1917, at Béthune, I made use of the then newly described method and apparatus introduced by Van Slyke (4), and obtained estimates of the sodium bicarbonate, or alkali reserve, of the blood plasma in wounded men suffering from the low arterial pressure which accompanies shock, hemorrhage, and gas-gangrene. The results given by the Van Slyke instrument are expressed in volumes per cent of carbon dioxid which can be separated from the plasma after it has been exposed to an atmosphere containing 5.5 per cent of the gas (the concentration existing in the pulmonary alveoli and present in the final air of an extreme expiration). Any figures lower than 50 volumes per cent carbon dioxid in the plasma of adults indicates a reduction of the alkali reserve below the normal range of variation. In the sense defined by L. J. Henderson (5) and by Van Slyke and Cullen (6), readings below this normal range may be regarded as marking a condition of "acidosis." The expressions "reduction of the alkali reserve" and "reduction of the carbon dioxid capacity" may be used interchangeably with reduction of blood alkali. In the Béthune cases, observations were made on the relation of reduced alkali reserve to blood

pressure, to pulse and respiration, and to other attendant conditions which will be reported later.

Relation of Reduced Alkali Reserve to Blood Pressure.—In 46 different coincident determinations of blood pressure and carbon dioxid capacity a rough relation between the two was found; in general the lower the blood pressure the lower the alkali reserve. This relation is illustrated in the following table:

TABLE III

RELATION BETWEEN CARBON DIOXID CAPACITY AND BLOOD PRESSURE

Number of Cases	Carbon Dioxid Capacity (Volumes per cent)		Systolic Arterial Pressure mm. Hg.
		Average	Average.
6	50 to 59	53	90
26	40 to 49	44	75
8	30 to 39	35	72
6	20 to 29	24	59

It is noteworthy that, in 39 of the 46 cases, the average systolic pressure was 75 mm. Hg. or less, and that in all these there was a carbon dioxid capacity of less than 50 volumes per cent, that is, below the normal range of variation. Furthermore, as the average carbon dioxid capacity was low, the average systolic pressure was likewise low. In Fig. 6 are presented the records of blood pressure, systolic and diastolic, in 34 cases in which the blood pressure was low, due either to shock, hemorrhage or gas-gangrene, and which have been arranged in the order of decreasing blood alkali. From this group, moribund patients and those who had received special treatment have been eliminated. In the first 6 cases there was a carbon dioxid capacity of 50 per cent or more; they are not to be regarded as abnormal. In the remaining 29 cases the blood pressure varies roughly in correspondence with the state of the blood.

In the above cases, some process that has brought about the state observed at admission of the patient, has been going on for hours, often six or eight. The progressive character of the process was shown in an instance in which the carbon dioxid capacity, one hour after the wounding, was 50 per cent, and five hours later, with no corrective treatment, it had fallen to 40 per cent. The condition has a gradual rather than an acute onset.

Relation of Reduced Alkali Reserve to Respiration.—The chemical stimulus which normally augments respiration is probably in the main an increase of the H-ion concentration in arterial blood. As L. J. Henderson (7) has shown, a large amount of acid may be added to a bicarbonate solution similar in concentration to that of the blood before any considerable increase of acidity occurs, so long as the carbon dioxid passes off. The H-ions of the blood do not increase to an important degree, therefore, in spite of reduced alkali, if pulmonary ventilation prevents an accumulation of carbonic

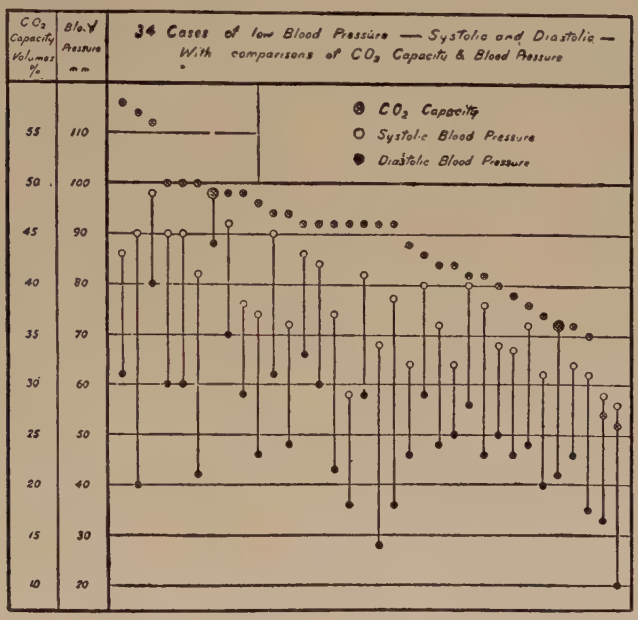

FIG. 6.—RECORDS OF BLOOD PRESSURE IN THIRTY-FOUR CASES OF SHOCK, HEMORRHAGE AND GAS BACILLUS INFECTION, ARRANGED IN THE ORDER OF DECREASING CARBON DIOXID CAPACITY.

acid. Only when this process fails, or acids increase to such an amount as seriously to encroach on the neutralizing bases of the blood plasma, does an increased H-ion content greatly affect the respiratory center. From a study of the alkali reserve by the Van Slyke method in a large number of surgical cases, Caldwell and Cleveland (8) reported no change of respiration when the carbon dioxid capacity lay between 43 and 50 per cent; and also none between 36 and 43 per cent when that condition was stationary; but if the reserve was *diminishing* and had reached that range of variation, hyperpnea was almost always apparent.

Unfortunately, at Béthune apparatus for measuring the volume of respired air was not available and observations had to be confined to the rate of breathing. In Table IV the chest and abdominal cases have been omitted, for in them the pain due to respiratory movement may modify the breathing in a way which complicates the influence of the blood.

TABLE IV

RELATION OF CARBON DIOXID CAPACITY TO RESPIRATION

Number of Cases	Carbon Dioxid Capacity (Volumes per cent)		Average Respiratory Rate per Minute
		Average	
17	40 to 49	44	24
7	30 to 39	35	28
6	20 to 29	24	44

As the figures show, the respiratory rate per minute increased as the alkali reserve fell; but the change, as was to be expected, became sharply augmented only as the limit of the reserve was more nearly approached. The character of the respiration was not noteworthy except in connection with marked reduction of the blood alkali, that is, only when there was a carbon dioxid capacity in the region of 30 volumes per cent or lower. In some of these instances the breathing was deep and vigorous, as in true "air hunger," and at the rate of 40 or 50 breaths per minute.

Explanation of the Diminished Alkali Reserve.—Two explanations have been offered to account for the reduction of the bicarbonate of blood plasma: one, that nonrespirable acid, such as lactic acid, develops in the tissues because of oxygen-want, and, uniting with the sodium of sodium bicarbonate, drives off carbon dioxid, which is breathed out; the other, that excessive respiration diminishes the carbonic acid in the blood with consequent *alkalosis,* and that thereupon the extra alkali disappears into the tissues, or diffuses into body fluids outside the blood, or escapes through the kidneys. The former process has been designated by Henderson as the "acidotic," the latter as the "acapnial" reduction of blood alkali.

There is a good deal of evidence that an insufficient oxygen supply to the tissues results in formation of lactic acid. Zillesson (9), 1891, noted that when the blood supply of the muscles or liver

was limited, lactic acid was formed in these organs. Araki (10) proved lactic acid (lactates) present in the urine of dogs and rabbits in conditions of oxygen-lack brought about by breathing carbon monoxid or by a low percentage of oxygen in the inspired air. In an artificially produced anemia, Irisawa (11) found that the lactic acid content of the blood increased as the oxygen-lack became more severe. More recently Milroy (12) and Penfield (13) have reported that reduction of blood alkali appears typically after a severe hemorrhage. And within the last few years, a number of workers have published papers on experimental shock in which there is agreement that a decreasing alkali reserve is associated with a falling blood pressure (McEllroy (14), Guthrie (15), Erlanger and Gasser (16) and Gesell (17). The low blood pressure in the late stages of experimental shock, according to Macleod (18), is associated with a demonstrable increase of lactic acid in the blood—an effect attributed by him to anoxemia because of depression of both the respiratory and the circulatory functions. All the conditions described above, which are associated with an increase of lactic acid or a reduced alkali reserve, are characterized by diminished blood volume, or diminished blood pressure, or decreased carrying power of the corpuscles, so that the delivery of oxygen to the tissues is reduced. It is well proved that in the absence of adequate oxygen supply, the lactic acid which accompanies muscular contraction, for example, is not burned to carbon dioxid and water (19). The liberation of such acid would produce the effects which have been observed—a demonstrable increase of lactates in the blood and a diminution of sodium bicarbonate. It may be, as Wertheimer, Fabre, and Clogne (20) have noted, that diacetic acid may also be present in some instances.

The other explanation for the reduced blood alkali, as stated above, attributes the change to relative increase of pulmonary ventilation. Henderson and Haggard (21) have reported that if they permit an animal to breathe to excess, as it naturally does during the development of shock from trauma of the abdominal viscera, failure of the circulation and death are induced. This is associated with a lowering of both the carbon dioxid content and the carbon dioxid capacity of the blood and also a lowering of the arterial pressure. In explanation of these results, Henderson and Haggard (22) have found that when animals are subjected to progressively decreasing oxygen percentages, the first effect is an abnormally large

loss of carbon dioxid from the body, due to excessive breathing, and that thereafter alkali passes out of the blood to compensate for the alkalosis thus developed. In other words, when the carbonic acid of the blood is lowered, sodium bicarbonate also falls. A modification of this view has been suggested by Moore (23) who assumes that as a consequence of shock there is a general lowering of metabolic activity to about one-third the normal rate. If now the lungs continue functioning at their usual rate or even less, there will be removed from the blood an excess of carbon dioxid over that which is produced, and the blood will be altered in the alkaline direction. Thereupon the kidneys and tissue cells remove alkali from the circulation; and if the blood is examined for circulating sodium bicarbonate, a lower figure than the normal is obtained.

With reference to the argument in the foregoing explanations, we may admit at once that excessive breathing due to oxygen-want may have the effect which Henderson has reported. Further, we may admit that in the presence of an excess of alkali, the tendency of the tissues and of the kidneys, in case there is sufficient blood pressure to permit them to act effectively, would be to remove the excess from the blood stream. There is some question, however, whether the hyperpnea assumed by Henderson, or the continued normal breathing in the absence of adequate stimulation (that is, the normal carbonic acid content of arterial blood) assumed by Moore, are actually present in cases of shock in human beings. Certainly the method of inducing excessive respiration in experimental shock which Henderson employed, that of positive overventilation of the lungs or vigorous manipulation of the diaphragm, does not represent the conditions attending the onset of shock as seen in man. The classic descriptions of shock refer to respiration as being shallow and feeble, interrupted by occasional sighs. Such was the character of the breathing noted in numerous cases of shock at Béthune. The rate, as shown in Table IV, tends to be much more rapid than normal; but since the breathing is shallow, the result is not likely to be an effective ventilation of the lungs (24). In three cases of shock in man observed by Aub (25), the ventilation per minute ranged between 5.77 and 7.19 liters per minute. In three other wounded men with normal blood pressures, the average figure was 8.2 with a range from 6.81 to 9.59 liters per minute. It is unfortunate that it was impossible to obtain more evidence regarding the volume of ventilation. If respiration is

shallow, however, it seems probable that there would be no reduction, or relatively slight reduction, of the alveolar carbon dioxid, and a consequent lessening of the concentration of carbon dioxid in the blood. According to Henderson and Haggard (26), morphin, by depressing respiration, tends to cause accumulation of carbonic acid in the blood, and therefore prevents the lowering of the alkali reserve. In the cases of human shock, as observed in Béthune, morphin was given as a routine procedure shortly after the men were wounded. In Table V are presented figures showing the systolic and diastolic blood pressures, the carbon dioxid capacity and the morphin dosage in 11 typical cases. These figures demonstrate that prompt administration of morphin even in doses of one-half grain, may not prevent a reduction of the alkali reserve.

TABLE V

CARBON DIOXID CAPACITY IN A SERIES OF SHOCK CASES TREATED WITH MORPHIN

Blood Pressure		CO_2 Capacity, (Volumes per cent)	Morphin Dosage gr.
Systolic	Diastolic		
92	70	49	$\frac{1}{4}$
78	56	30	$\frac{1}{2}$
64	40	21	$\frac{1}{2}$
76	46	41	$\frac{1}{4}$
42	28	40	$\frac{1}{4}$
72	48	38	$\frac{1}{2}$
80	58	43	$\frac{1}{4}$
56	20	26	$\frac{1}{4}$
92	62	47	$\frac{1}{4}$
68	42	36	$\frac{1}{2}$
75	46	36	$\frac{1}{4}$

Besides doubt as to whether excessive respiration is present in human shock, there is further question whether it would have, if present, a causal relation to the onset of the shock state. Aub (25), found that the volume of respiration per minute, in experimental shock produced by muscle injury, increased in 10 experiments 54 per cent above the average for the controls. This was, however, before the onset of shock. When the condition of shock

became established, the increase was only 14 per cent above the controls. One might assume that this indicated that the increased volume of respiration was causally related to the development of low blood pressure. Aub repeatedly observed, however, a rapid breathing with a large increase of the ventilation rate per minute under urethane anesthesia without the onset of shock. Furthermore, uniform artificial respiration may be given to an animal while passing into the state of shock, and under these circumstances no diminution of the carbon dioxid capacity of the plasma occurs until the blood pressure falls. Thus the respiratory factor is not permitted to vary and the excessive respiration, as postulated by Henderson, is therefore unable to produce the changes which he regards as the consequence of hyperpnea. Nevertheless, a low pressure develops, and as the pressure continues to fall there is a reduction of the alkali reserve. In one such instance, the blood pressure fell in half an hour from 110 to 40 mm. Hg. with a decline in carbon dioxid capacity of 12 volumes per cent. In the later stages of this fall of pressure there might have been a lessening of the CO_2-content of the blood because of uniform respiration in the presence of diminished metabolism, but the original drop of pressure could hardly be accounted for on the basis of hyperpnea. From all this evidence, it seems probable that the conditions Henderson established in his experiments do not account for the results observed in human cases, and that the reduced alkali may be explained as a consequence of diminished volume-flow to the tissues.

So far as Moore's contentions are concerned, there is no evidence, as we shall note later (see p. 76), that the metabolism in shock is reduced to any marked degree until there is a considerable fall of arterial pressure. In other words, the low metabolism may reasonably be regarded as a consequence of the diminished oxygen supply. The reduction of the alkali reserve which has been observed to accompany a diminished oxygen supply may be satisfactorily explained, therefore, on that basis, rather than on the assumption that with continued normal respiration and a diminished carbon dioxid production, a primary alkalosis results, followed by escape of the excess alkali.

The Significance of Reduction of the Alkali Reserve in Shock.—Experiments by Dale and Richards (27) and also by Gesell (28) have shown that a large amount of acid may be injected into the blood stream and the alkali reserve thereby reduced to a low degree

without any fall of blood pressure to a shock level. The concomitant fall of blood pressure and reserve alkali in shock, therefore, should not be regarded as indicating that a cause of shock is to be found in the lessened alkali content of the blood. Perhaps when this process reaches an extreme degree, there may be an increase of the H-ion concentration and a consequent damage to the tissues from the altered state of the blood; but in any moderate alteration of the blood, such as occurs in most cases of shock, it is probable that the diminished alkaline content in itself has no harmful influence.

On the other hand, no matter how the reduction of the alkali reserve is accounted for—either as a consequence of excessive production of acid or as a consequence of over-breathing, due to oxygen want—it is an indication of a fundamental difficulty occurring in the body, namely, an insufficient oxygen supply. I have already pointed out the extreme sensitiveness of nerve cells in the brain to lack of oxygen. The failure of delivery of sufficient oxygen to the brain is likely to affect profoundly the normal metabolism of nerve cells in particular, and to lead to a disturbance of their functions. It becomes a matter of importance, therefore, to know at what point in an impaired circulation the oxygen delivery to organs becomes inadequate.

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CHAPTER IX

THE CRITICAL LEVEL IN A FALLING BLOOD PRESSURE

Although a reduction of blood volume affects to a great degree the volume-flow of blood to peripheral organs, as Gesell has proved, it is interesting to note that in several of the experiments which he reports (1, Figs. 3 and 4) there is no marked reduction of the carbon dioxid content of the arterial blood in a series of determinations until the blood pressure falls to the neighborhood of 80 or 90 mm. Hg. Raymund (2, Figs. 2, 3, and 5b) likewise has reported cases of experimental shock in which, after the initial reduction of the blood alkali attributable to etherization, a further reduction does not take place until the blood pressure falls below approximately 80–90 mm. A similar relation is seen in several experiments performed by Henderson and Haggard (7, p. 365). These results are in interesting agreement with both experimental and clinical studies which were carried on by the group in France. This concordant testimony has practical importance. In the first place, it signifies that, though the reduced volume-flow is a highly disturbing element, the final touch in rendering the circulation inefficient is ascribable to a slowing of the blood flow as the arterial head of pressure falls. In the second place, the observation has significance because of the ease of determining the head of arterial pressure by clinical means and thus having a basis for judgment as to whether the impairment of the circulation has reached a dangerous degree.

Experimental Determination of the Critical Level.—In order to produce experimental conditions which would be as closely as possible analogous to those which analysis has shown to be true for shock, and yet preserve the possibility of controlling accurately these conditions, Cattell and I made use of the arrangement illustrated in Fig. 7, a modification of the method employed by Johansson and Tigerstedt (3) for recording the volume changes of the heart. Under artificial respiration, the thorax was opened between the ribs on one side at the level of the lower end of the

sternum. A small slit was cut in the pericardium and a glass cannula tied in place. The thorax was now tightly closed and the animal allowed to breathe naturally. A small funnel was connected with the cannula by means of rubber tubing and filled with normal salt solution or with 6 per cent gum acacia in normal saline. The pressure of the column of fluid was transmitted to the outside of the heart in the pericardial sac, and thus affected directly the filling of the organ and consequently its output. By raising or lowering the funnel, any desired arterial pressure could be produced and maintained. In a few experiments the arterial pressure was regu-

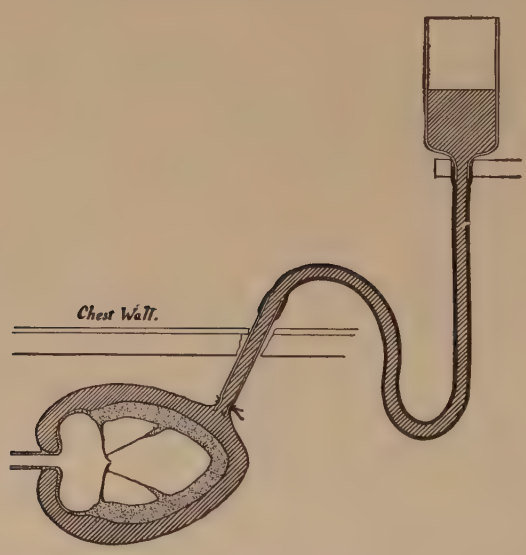

FIG. 7.—ARRANGEMENT FOR CONTROLLING THE CARDIAC OUTPUT AND CONSEQUENTLY THE HEIGHT OF ARTERIAL PRESSURE BY MEANS OF INCREASING OR DECREASING INTRA-PERICARDIAL PRESSURE.

lated by compression of the heart by means of a clamp applied to the chest. This method gave similar results, but was inferior because it interfered with the respiratory movements.

Most of the experiments were performed on cats, but in a few cases rabbits or dogs were used. Ether was found to be a satisfactory anesthetic, for preliminary observations showed that under the conditions of our experiments it produced no effect on the alkali reserve. A cannula was placed in the pericardium to control the arterial pressure, as described above. The blood pressure was recorded by a mercury manometer connected with one carotid; a

second cannula was placed in the other carotid or in the femoral artery to obtain samples for the bicarbonate determinations. For each determination about 3 c.c. of blood were taken in a graduated tube, centrifuged, and the alkali reserve of the plasma determined by the Van Slyke method (4). A sample of blood was usually taken immediately before reducing the blood pressure and at intervals of an hour throughout the course of the experiment. Usually no difficulty was experienced in keeping a constant arterial pressure at any desired level. Sometimes, just after reducing the pressure, it was necessary to adjust the funnel repeatedly in order to hold the arterial pressure constant, but usually an equilibrium was reached in a short time. A few experiments had to be discarded on account of irregularities in pressure.

Throughout the whole series of observations a satisfactorily constant relation was found between the degree of reduction of the alkali reserve and the lowering of blood pressure; the most marked reduction was found at low pressures, whereas above 80 mm. Hg. the state of the blood remained quite unchanged. These differences can be shown by a few illustrative protocols:

EXPERIMENT II, MAY 10, 1918—CAT.—3.5 KILOS.

Ether. Cannula in both carotids
10:08 B. p. 178 mm. T. 36° C.
10:22 B. p. 160 mm.
10:23 Sample A. 3 c.c. blood. CO_2 reading, 39 vols. per cent.
10:24 B. p. 160 mm.
10:26 Arterial pressure reduced to 80 mm. by external pressure on chest.
11:27 Sample B. 3.2 c.c. blood. CO_2 reading, 37.
12:24 Sample C. 3.0 c.c. Sample lost.
12:57 Sample D. 3.5 c.c. CO_2 reading, 38.
1:29 Pressure reduced to 60 mm.
2:38 Sample E. 2.7 c.c. CO_2 reading, 35.
3:01 Pressure removed from thorax. B. p. gradually rose until 4:00 when it reached 112 mm. Hg.
4:01 Sample F. 4.5 c.c. CO_2 reading, 40.

EXPERIMENT III, MAY 11, 1918—CAT.—2.9 KILOS.

Ether. Cannulas in both carotids. Cannula in pericardium.
9:51 B. p. 124 mm.
9:53 Sample A. 5.0 c.c. CO_2 reading, 30.
10:00 B. p. fell to 80 mm. Kept at the level by intrapericardial pressure.
11:02 Sample B. 4.5. c.c. CO_2 reading, 31.

11:04 Pressure reduced to 60 mm.
12:03 Sample C. 4.0 c.c. CO_2 reading, 20.
12:08 Intrapericardial pressure removed. B. p. rose to 116 mm. Hg.
12:31 Sample D. 4.0 c.c. CO_2 reading, 25.
12:32 Pressure reduced to 70 mm.
1:31 Sample E. 4.5 c.c. CO_2 reading, 23.

EXPERIMENT XVI, MAY 25, 1918—Dog—6.73 KILOS.

7:35 Morphia 0.056 gram.
8:45 Operation started. Cannula in pericardium. Carotid cannulas.
9:50 Sample A. 3.0 c.c. CO_2 reading, 33.
9:52 B. p. 120 mm.
10:12 B. p. 116 mm.
10:17 B. p. reduced to 60 mm. by intrapericardial pressure (gum salt).
11:17 Sample B. 4.5 c.c. CO_2 reading, 22.
12:22 Sample C. 6.0 c.c. CO_2 reading, 20.
1:22 Sample D. 6.2. c.c. CO_2 reading, 19.
2:31 Sample E. CO_2 reading, 20.

The results for the series of experiments are summarized in Tables VI to XI which follow. Cases in which the blood pressure was reduced to 80 mm. Hg. are given in Table VI. In every case the alkali reserve was unaffected by an hour at this pressure. Table VII shows the effects at 70 mm. pressure. Here there is a slight reduction in the alkali reserve—an average fall of 3 volumes per cent of carbon dioxid. In the two cases in which observations were continued for four hours, a recovery took place. This occurred in a certain number of cases, even at lower blood pressures; the phenomenon will be referred to again. The next two tables give the results for an arterial pressure reduced to 60 mm. Hg.—Table VIII giving figures for cases in which the low pressure was continued for only one hour, and Table IX for cases of low pressure for three hours. With this pressure it will be noted that there was a marked fall in the alkali reserve during the first hour, indicating that the circulation was no longer adequate to maintain normal oxidation in the body. During the second hour, the average of the results shows a slight further fall, but during the third hour there is no further change. Table X, giving effects of the reduction of the blood pressure to 50 mm. Hg., reveals a still greater fall in the alkali reserve; at the end of one hour the volume per cent of CO_2 reached the low figure of 20.5.

TABLE VI

BLOOD PRESSURE REDUCED TO 80 MM. HG.

Experiment	Animal	Orig. B. P.	Alkali Reserve			
			Start	1 Hour	2 Hours	3 Hours
May 10	cat	178	39	37		38
11	cat	124	30	31		
15	dog	80	35	35		
16	dog	160	20	20	17	
		Average	31.0	30.8		

TABLE VII

BLOOD PRESSURE REDUCED TO 70 MM. HG.

Experiment	Animal	Orig. B. P.	Alkali Reserve				
			Start	1 Hour	2 Hours	3 Hours	4 Hours
May 11	cat	116	25	23			
13	cat	170	33	31	25		
27	cat	142	30	27	32	34	35
June 14	cat	168	34	29	29	32	33
		Average	30.5	27.5			

An examination of the data presented in the foregoing tables shows a normal bicarbonate reserve in the cat of from 39 to 25, the average being about 32. This is a much lower figure than that found in normal human plasma, where a reading below 50 is generally considered to be pathological. The most rapid fall in the alkali reserve occurs during the first hour of reduced pressure, after which it soon reaches a stationary low level. In a few individual cases there is an actual recovery after several hours. It may be that by lessened cellular activity the organism adapts itself to the condition of low pressure; and then, because the oxygen requirement becomes less, the acids present may be reduced by oxidation.

TABLE VIII

BLOOD PRESSURE REDUCED TO 60 MM. HG. FOR ONE HOUR

Experiment	Animal	Orig. B. P.	Alkali Reserve		
			Start	1 Hour	2 Hours
May 10	cat	178	38	35	
11	cat	124	31	20	
24	rabbit	...	27	18	
June 5	cat	...	37	20	
July 15	cat	136	30	19	18
16	cat	114	26	19	
		Average	31.5	21.8	

TABLE IX

BLOOD PRESSURE REDUCED TO 60 MM. HG. FOR THREE HOURS

Experiment	Animal	Orig. B. P.	Alkali Reserve				
			Start	1 Hour	2 Hours	3 Hours	4 Hours
May 9	cat	130	39	36	32	32	
25	dog	120	33	22	20	19	20
29	cat	128	35	32	33	33	
June 13	cat	140	31	14	18	19	
July 13	cat	118	37	29	29	27	29
20	cat	109	33	30	25	27	
		Average	34.7	27.1	26.1	26.1	

Since our experiments were completed, another possibility has suggested itself, but too late to permit us to judge conditions. Clearly, if the pressure is artificially kept constant throughout an experiment, it is possible that after several hours a peripheral dilatation takes place, due to lessened vasomotor tone or to direct effect of metabolites, and thus with a constant pressure the blood flow would be increased.

TABLE X

BLOOD PRESSURE REDUCED TO 50 MM. HG.

Experiment	Animal	Orig. B. P.	Alkali Reserve			
			Start	1 Hour	2 Hours	3 Hours
May 28	cat	174	27	14	11	
June 5	cat	...	37	19		
July 18	cat	86	28	20	23	21
23	cat	96	41	29		17
		Average	33.2	20.5		

The alkali reduction produced by an inadequate circulation is not permanent, but rapidly disappears when the blood pressure is allowed to return to normal, as is shown above in the first two protocols (see p. 65). In a number of other instances the blood pressure was raised by injection of gum-salt solution and the alkali reserve was restored.

Many cases of low blood pressure in wounded men are complicated by hemorrhage. The question arose as to whether loss of blood modified the critical level of the blood pressure. This was somewhat difficult to determine experimentally because in many animals the combination of an operation and the loss of blood reduces the blood pressure below the desired level. Satisfactory results were obtained in four animals (see Table XI). In each case

TABLE XI

PRESSURE REDUCED TO 80 TO 90 MM. HG. AFTER REMOVING 20 PER CENT OF BLOOD

Experiment	Blood Pressure		Alkali Reserve		
	Original	Final	Start	1 Hour	2 Hours
May 14	175	80	31	26	23
21	150	80	20	16	
23	100	90	37	35	35
June 16	150	90	33	33	

they were bled 20 per cent of their calculated blood volume before reducing the pressure. The two cases with arterial pressure reduced to 80 mm. Hg. show marked indications of an inadequate circulation, while those with a reduction to only 90 mm. show less effect. It seems probable, therefore, that when hemorrhage complicates a

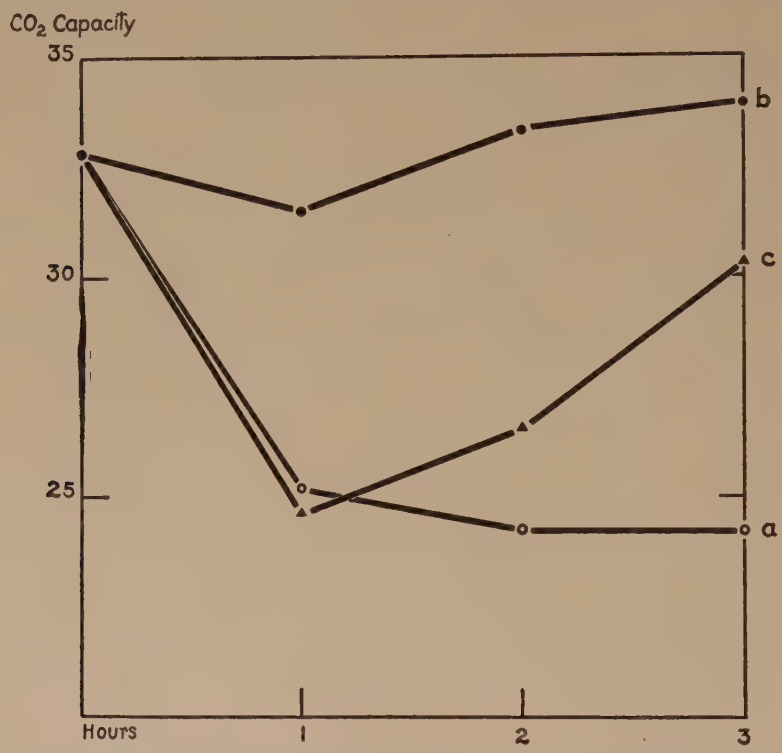

FIG. 8.—CHANGES IN PERCENTAGE BY VOLUME OF CARBON DIOXID (THE ALKALI RESERVE) OF THE BLOOD PLASMA. These changes took place in cases in which the blood pressure was lowered to 60 millimeters of mercury for three hours; in *a* without other action, in *b* with previous injection of morphin, and in *c* with morphin injected after one hour of low pressure.

low blood pressure, the critical level is higher than when no loss of blood has occurred.

From these experimental results we conclude that the *critical level,* that is, the level at which the blood pressure is no longer capable of maintaining an adequate volume-flow to the tissues, and thus serving the normal oxidations of the body, is *approximately 80 mm. Hg.* Above 80 mm. reduction of the alkali reserve is not likely to appear, but as the pressure falls below this, a reduction will probably occur, which is more marked and develops the more rapidly, the lower the pressure.

If there has been a loss of blood, the circulation becomes inadequate before the pressure falls to 80 mm. Hg., that is, the critical level is raised. In this connection the observations of Markwalder and Starling (5) are of interest. They found experimentally that cardiac contraction begins to weaken when the arterial pressure falls below 90 mm. Hg. Gruber (6) noted a marked decrease in the height of contraction of muscle which was being uniformly stimulated when he reduced the blood pressure to 90 mm. Hg. Above this level, however, changes in pressure produced practically no effect on muscular contraction. The results reported by Gesell, by Raymund and by Henderson and Haggard, mentioned above, likewise point to a pressure of 80 or 90 mm. Hg. as being necessary for a sufficient blood flow.

The Effect of Morphia.—As shown in Table IX, reduction of the blood pressure to 60 mm. Hg. for three hours causes a marked and lasting reduction of the alkali of the blood plasma. Experiments performed by Cattell at Dijon proved that morphia can modify this effect in a striking manner. A comparison of the average figures in Tables XII and XIII with those in Table IX is given graphically in Fig. 8. The graphs of each condition have been shifted so that they have a common initial point at the average of the first readings (32.8). Graph (*a*) represents the results detailed

TABLE XII

MORPHIN GIVEN ONE HOUR AFTER REDUCTION OF BLOOD PRESSURE TO 60 MM. HG.

Experiment	Animal	Orig. B. P.	Alkali Reserve				
			Start	1 Hour	2 Hours	3 Hours	4 Hours
June 7	dog	138	24	15	11	12	18
8	dog	128	23	16	20	22	23
10	cat	150	35	21	27	29	34
17	cat	120	35	35	37	42	
18*	cat	118	30	20	21	31	
19*	cat	150	32	23	23	28	
20	cat	156	36	21	23	22	22
24	cat	120	26	24	29	35	36
		Average	30.1	21.9	23.9	27.6	

TABLE XIII

MORPHIN GIVEN JUST BEFORE REDUCING BLOOD PRESSURE TO 60 MM. HG.

Experiment	Animal	Orig. B. P.	Alkali Reserve				
			Start	1 Hour	2 Hours	3 Hours	4 Hours
June 26	cat	100	32	34	39	37	35
27	cat	134	35	32	36	37	39
29	cat	142	29	27	27	31	33
July 8	cat	114	41	33	35	34	
Oct. 27*	cat	128	30	34	33	32	
29*	cat	120	34	33	34	37	35
		Average	33.5	32.2	34.0	34.7	

in Table IX—a fall and continued low level of the blood alkali when the blood pressure is held down to 60 mm. Hg. Graph (*b*) represents Table XIII, and (*c*), Table XII. In the former case morphin sulphate (20 mg. per kilo) was given subcutaneously just before the pressure was lowered; the alkali reserve was not reduced. In the latter case it was given after the pressure had been kept at 60 mm. for one hour; the alkali reserve, which had fallen as in (*a*), began to rise and after two hours was largely restored.

The explanation of this conserving influence of morphia is still obscure. Henderson and Haggard (7) have reported that when, by means of morphin, respiration is depressed and the alveolar CO_2 is raised, the alkali reserve of the blood also rises and they suggest that this rise is due to a passage of alkali from the tissues into the blood to compensate for the increase in carbonic acid. The reactions represented in graphs (*b*) and (*c*), however, occur in animals in which the breathing is kept mechanically regular by artificial respiration. In Table XII the experiments of June 18 and 19, and in Table XIII the experiments of October 27 and 29 (marked by asterisks) were of this character. They do not differ in nature from the other experiments of the series in which the respiratory mechanism of the animal was permitted to function. It seems, therefore, that slowing of the respiration is not solely responsible for the preservation of the normal alkali reserve.

Possibly morphia, by reducing the activity of tissues, lessens their demand for oxygen and thus compensates for the smaller supply of

oxygen in the sluggish blood flow. Further experiments are needed, however, before this suggestion should be accepted.

Clinical Evidence for a Critical Level.—After obtaining the foregoing experimental indications of a critical level, I went over the Béthune records of low blood pressure in cases of shock and hemorrhage, in which determinations of the alkali reserve had been made simultaneously. These records were then tabulated on the basis of systolic blood pressure. The figures are given in Table XIV. As the Table shows,

TABLE XIV

RELATION OF CARBON DIOXID CAPACITY TO SYSTOLIC BLOOD PRESSURE IN FORTY-THREE CASES OF SHOCK AND HEMORRHAGE

Systolic Blood Pressure	Av. CO_2 Capacity (Volumes per cent)	Variation	Number of Cases
96–102	48	40–56	5
90– 92	49	41–58	7
82– 86	49	43–52	5
72– 78	43	30–49	10
62– 68	36	21–42	11
52– 59	24	20–27	5

the alkali reserve rarely falls below the normal (approximately 50 volumes per cent) until the systolic pressure lies below 80 mm. Hg. Furthermore, the greater the reduction of blood pressure below this critical level, the greater is the reduction of the carbon dioxid capacity or the alkali reserve.

The significance of these observations will become more manifest as we consider how the reduced pressure is related to metabolism in the body and to the damage suffered by sensitive structures when insufficiently supplied with oxygen.

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CHAPTER X

THE BASAL METABOLISM IN SHOCK

The evidence that as shock is developing the blood flow in most parts of the body is much reduced in volume, that this reduction becomes more marked as the head of arterial pressure falls below a critical level, and that then the alkali of the blood begins to decrease, we have interpreted as implying a deficient delivery of oxygen to the tissues. Thus the oxidative processes might be interfered with, and consequently there would be a profound effect on bodily metabolism. In 1917 Henderson, Prince, and Haggard (1) mentioned that metabolism is lowered in animals subjected to experimental shock. Early in the study of shock under battle conditions, it appeared desirable to learn whether metabolism is disturbed in man, and if so to what degree. In the spring of 1918 arrangements were started for securing data which would throw light on these questions, but owing to the great difficulty of assembling scientific apparatus, full preparations were not completed until late in September. About the middle of October, Lieutenant J. C. Aub was assigned to a forward hospital, which was receiving men from the Argonne sector, to conduct the studies. Before he had opportunity, however, to make more than preliminary observations, the War ended and the attempt to obtain information from an examination of human cases had to be given up. Lieutenant Aub was able, however, to pursue the studies under experimental conditions at the Harvard Physiological Laboratory, and thus the inferences and suggestions regarding metabolic disturbance, that were based on consideration of circulatory changes, have been put to the test (2).

Methods.—In the experiments carried on by Aub, cats, which had not been allowed to take food for the previous twenty-four hours, were used. They were anesthetized by urethane given by mouth—8 c.c. of a 25 per cent solution per kilo of body weight. A study of the metabolism following urethane anesthesia alone showed that it remained constant for at least four and one-half hours. Thereupon it might fall to a lower level. Raeder (3), who kept

rabbits under urethane for three days during which he studied their metabolism, concluded that it fell only about 2 per cent per hour. Urethane appears to be, therefore, a satisfactory anesthetic to employ in studying respiratory metabolism. Its advantage over any volatile anesthetic lies, of course, in the freedom of the respiratory gases from the presence of the anesthetic. After being anesthetized the animals were placed on a heating pad and the temperature kept as nearly constant as possible.

The operation consisted of inserting a tracheal cannula, two arterial cannulas (usually into the carotids), and usually also another into the external jugular vein. One of the carotid cannulas served to connect the circulation with the mercury manometer for recording blood-pressure changes.

The samples of expired air were obtained in two 8-liter copper spirometers. The air sample was promptly withdrawn from the spirometer and preserved under pressure in a glass sampling tube. Gas analyses were made in the Haldane gas apparatus; careful checks of room air were made before the samples were analyzed. To produce shock the method was used which Bayliss and I devised, namely, that of injuring the muscles of the hind legs (see p. 144). When the blood pressure fell below 70 mm. Hg. and remained below that level the animal was regarded as being in a state of shock. All extra manipulation after the trauma was carefully avoided.

The Effects of Shock on Basal Metabolism.—As shown by experiments XXVI and XXVII in Table XV, the basal metabolism alters to only a slight degree under urethane anesthesia when there is no disturbance of the circulation. In these and in other cases, the basal metabolism is not calculated in terms of unit area of body surface, since the comparison is made not between individual instances but between the conditions of the same individual before and after shock is induced.

The level of basal metabolism after the establishment of shock was invariably lower than the level before shock was produced. In 8 cases of mild experimental shock the average fall in the number of calories per hour was 18.5 per cent, and in 8 cases of severe shock the average fall was 33 per cent. An example of mild shock is seen in experiment L of Table XV. Examples of more severe shock are given in experiments XXXVI and XXXVIII.

That the diminished blood pressure in shock is itself an important element in reducing the metabolism was readily proved. The

pressure was lowered and kept low by increase of intrapericardial tension as has been previously described (see p. 64). In five cases in which this was done, the average drop in metabolism was found to be similar to that in shock, namely, 31 per cent. An example of such an experiment will be found in case XLIX, Table XV.

It was a matter of interest to learn whether the fall of metabolism was related in any way with the critical level of arterial blood pressure, as indicated by reduction of the alkali reserve. Aub found, indeed, that as a rule the critical level for metabolism was associated with a blood pressure in the neighborhood of 75 or 80 mm. Hg. At that level, the metabolism might be within the normal range of variation, but usually, when this was the case the blood pressure had been remaining stationary or was rising. In other instances, he noted that when the blood pressure was at this level, or occasionally higher, the metabolism might be considerably reduced, but when this was the case the blood pressure was in the process of falling. With a blood pressure below 75 mm. Hg., the metabolism was invariably reduced beyond the common normal variations.

A curious and somewhat anomalous observation was that when the blood pressure is lowered by hemorrhage alone, the low level may not be associated with a marked reduction of metabolism. Thus, in one case of hemorrhage, after the blood pressure had remained at 50 mm. Hg. for 20 minutes but was rapidly rising at the time the gas sample was taken, the metabolism was reduced only 7 per cent. (See case XXXIV, Table XV.)

The Oxygen Content of Venous Blood in Shock.—The anomalous instances mentioned above, those in which the metabolism after trauma was considerably reduced though the pressure was in the neighborhood of the critical level or above it, and those in which the metabolism after hemorrhage was only slightly reduced though the pressure had been much below the critical level, suggest that variations of volume-flow, not revealed by blood pressure, were accountable. Thus, after trauma, though the blood pressure is at 80 mm. Hg. or above, but falling, the volume-flow may be greatly reduced; whereas after hemorrhage, with a pressure of 50 mm. Hg., but rising, the volume-flow may be more nearly adequate to the tissue needs. In order to obtain further insight into the adequacy of the oxygen supply, Aub and Cunningham estimated the oxygen content of venous blood at different stages of experimental shock.

They found that before the blood pressure had fallen to a shock level, the O_2 content of venous blood might be greatly reduced below normal (see Fig. 9). This observation is in harmony with the evidence presented by Gesell (4) that, after reduction of blood volume but before any fall of blood pressure, there may be so great a constriction of peripheral vessels, as shown by the submaxillary gland, that the volume-flow through them is much diminished. In

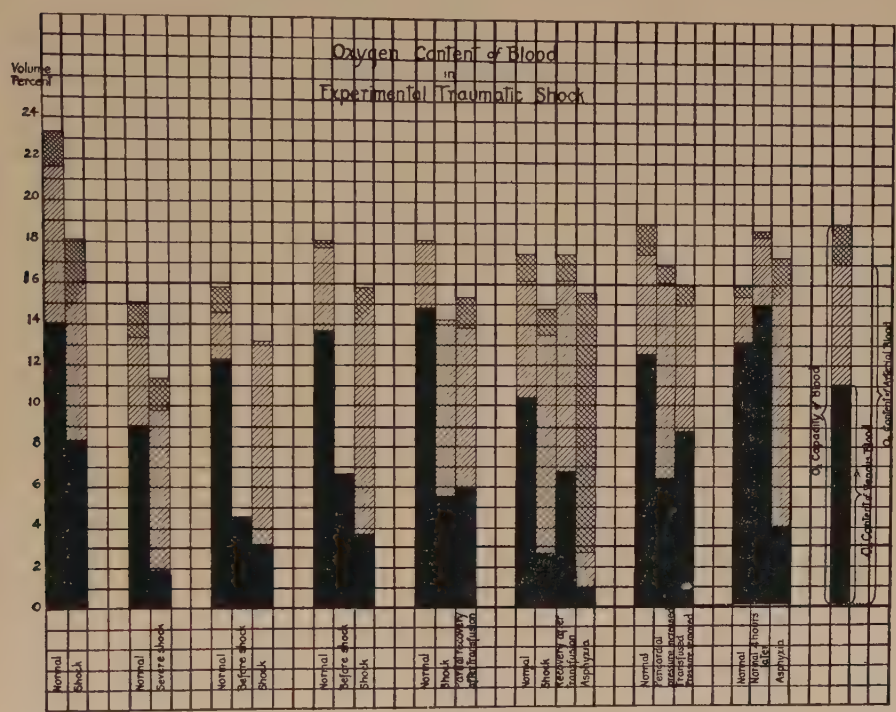

FIG. 9.—NORMAL = ANIMAL UNDER URETHANE ANESTHESIA. Before shock = After muscle trauma, but before a true shock level of blood pressure had been established. Asphyxia = Clamping off trachea completely for four or five minutes.

accordance with the recent work of Krogh (5) which indicates that closed capillaries will open if there is oxygen-want, it is clear that along with a constriction of arterioles there might be dilation of capillaries and consequently not only a reduced volume-flow, but also a slower rate of flow in them. Under such circumstances oxygen would be taken from the blood in much larger percentage than normally, and even so, might not be adequate to meet the basal needs of the tissues. Of course, as the head of pressure in the arteries begins to fall, because of a too great reduction of blood

volume, the inadequacy of oxygen delivery becomes more marked and consequently the decrease of metabolism is more striking. On the other hand, after hemorrhage, the blood volume is normally increased by passage of fluid from tissue spaces into the blood stream. When this has occurred to such a degree that the blood pressure is beginning to rise, it may well be associated with an increased speed of flow and consequently with an increased delivery of oxygen to the tissues. Under such circumstances even though arterial pressure is below the critical level, we might reasonably expect the metabolism not to be so greatly reduced as it is when shock is progressing.

The Effects of Transfusion.—Further evidence regarding the importance of the circulation to normal metabolism is found in the effects of transfusion. When an animal which has been brought into a state of shock is transfused with blood, the effect on metabolism depends on the consequences of the transfusion. If the transfusion causes a permanent restoration of blood pressure, the metabolism promptly returns to its normal level (experiments XLVII and XLVIII, Table XV). On the other hand, if transfusion does not permanently restore blood pressure, the metabolism remains low (experiment XLI, Table XV).

The evidence presented above is confirmatory of the view which has been developed in previous chapters, that the primary consequence of diminished blood volume and lowered blood pressure is such a great reduction in the volume-flow of blood to the tissues of the body that the oxygen supply becomes inadequate. Evidence regarding the damage which results from this insufficient delivery of oxygen will be presented in a later chapter. At present the point to be emphasized is that when the oxygen delivery becomes inadequate, the heat production of the body is markedly lowered. In severe shock, as mentioned above, the number of calories may be reduced fully one-third. This is an important observation, because of the well-known relationship between cold and shock.

TABLE XV

CONTROLS

Experiment, Weight, Date	Time of Period	CO_2 per Minute, c.c.	O_2 per Minute, c.c.	Resp. Quot.	Calculated Calories per Hour		Resp. Rate per Minute	Resp. Vol. per Minute, c.c.	Rectal Temperature C. °	Blood Pressure mm. Hg.	Blood CO_2 Combining Power Vol. Per Cent
					Cal.	Per Cent Var.					
XXVI	11:35	19.4	28.3	0.69	7.83	....	62	583	38.0	95–105	
3200 gms.	12:07	21.2	27.9	0.76	7.90	....	....	615	....	110	
28/3/19	12:50	20.2	28.6	0.71	8.03	....	44	587	37.0	120–110	
	2:00	19.9	27.7	0.73	7.78	− 1	46	606	36.5	110	
	3:00	22.0	28.8	0.76	8.18	+ 4	Dyspnœa	694	36.8	115–120	
	4:00	19.7	26.1	0.75	7.38	− 6	46	474	36.8	120	
	5:10	18.7	26.6	0.70	7.45	− 5	....	447	37.6	110	
XXVII	12:23	....	....	....	....	....	....	478	36.8	160	47.1
3100 gms.	1:23	19.8	25.9	0.76	7.35	....	20	369	36.4	150	
31/8/19	2:25	19.8	26.1	0.76	7.39	+ 0.6	....	427	36.6	130	
	3:30	18.7	25.8	0.72	7.25	− 1.7	....	366	37.0	135	
	4:25	18.9	25.5	0.74	7.19	− 2	....	342	37.0	135	
	5:25	17.8	24.4	0.73	6.84	− 7	27	328	36.5	115	53.8
MILD SHOCK											
L	12:05	22.3	31.0	0.72	8.70	....	18	613	38.9	128	
4600 gms.	12:25	21.6	30.9	0.70	8.67	....	20	608	38.8	120	
10/12/19	2:48	22.1	27.5	0.80	7.87	− 9	....	950	38.3	73	
	3:11	21.1	24.5	0.86	7.11	−18	29	1241	38.6	72	

TABLE XV—*Continued*

SEVERE SHOCK

Experiment, Weight, Date	Time of Period	CO_2 per Minute, c.c.	O_2 per Minute, c.c.	Resp. Quot.	Calculated Calories per Hour		Resp. Rate per Minute	Resp. Vol. per Minute, c.c.	Rectal Temperature C. °	Blood Pressure mm. Hg.	Blood CO_2 Combining Power Vol. Per Cent
					Cal.	Per Cent Var.					
XXXVI	11:48	11.1	15.8	0.70	4.44	....	40	391	37.1	135	
2400 gms.	12:20	10.6	15.6	0.68	4.38	....	36	369	36.8	100–130	
26/4/19	1:45	11.1	14.4	0.77	4.10	− 7	34	408	37.3	75	
	2:45	9.4	11.4	0.82	3.23	−26	36	409	36.9	80–75	
	3:30	8.2	11.3	0.73	3.28	−26	30	292	36.9	60–63	
XXXVIII	11:45	13.4	17.7	0.76	5.00	....	30–26	362	36.2	140	
2400 gms.	12:17	13.5	18.0	0.75	5.08	....	28–50	377	36.3	100	
1/5/19	1:12	11.5	16.5	0.70	4.63	− 8	30	400	36.2	80	
	2:22	16.4	20.2	0.81	5.80	+15	72–66	1212	36.4	80	
	3:25	10.4	12.5	0.83	3.61	−28	46	720	35.6	65	
	3:45	7.1	9.8	0.73	2.74	−46	22	377	35.7	60	
PERICARDIAL PRESSURE											
XLIX	3:34	8.6	13.8	0.62	3.89	....	43	252	36.2	90	
2500 gms.	3:58	10.3	13.9	0.74	3.90	....	46	258	36.4	93	
25/7/19	4:25	9.5	11.7	0.81	3.37	−13	38	285	36.5	55	
	4:44	9.0	10.6	0.85	3.07	−21	40	278	36.6	58	
	5:03	8.8	10.6	0.83	3.06	−21	42	296	36.8	59	

HEMORRHAGE

Experiment, Weight, Date	Time of Period	CO_2 per Minute, c.c.	O_2 per Minute, c.c.	Resp. Quot.	Calculated Calories per Hour		Resp. Rate per Minute	Resp. Vol. per Minute, c.c.	Rectal Temperature C. °	Blood Pressure mm. Hg.	Blood CO_2 Combining Power Vol. Per Cent
					Cal.	Per Cent Var.					
XXXIV	11:15	14.7	20.4	0.72	5.73	....	44	523	36.2	102	48.3
2700 gms.	11:35	13.0	18.4	0.71	5.15	−10	40	464	36.3	55–62	
19/4/19	12:15	14.4	19.8	0.71	5.65	− 1	47	482	36.3	75–80	
	12:45	15.2	19.1	0.80	5.45	− 5	46	536	36.4	82	
	1:45	15.0	20.2	0.74	5.69	− 1	51	506	35.6	110	
	2:30	14.8	18.6	0.80	5.32	− 7	40	637	35.8	65–85	52.0

TRANSFUSIONS

XLVII	1:22	17.2	22.0	0.78	6.27	....	51	571	37.1	92	
2600 gms.	2:20	14.6	21.6	0.67	60.7	....	63	660	36.7	105	
17/7/19	3:43	14.8	21.6	0.96	6.06	− 2	64	692	36.3	82	
	4:05	16.1	17.7	0.91	5.20	−16	83	967	36.4	75–65	
	4:17	12.3	15.7	0.78	4.47	−28	72–176	944	36.2	50–70	
	4:48	13.5	17.7	0.75	4.98	−19	40	493	35.2	95–105	
	5:19	12.7	21.0	0.61	5.88	− 5	46	476	36.3	110	
	5:38	14.1	19.7	0.72	5.58	−10	42	482	36.5	105	

TABLE XV—*Continued*

TRANSFUSIONS—*Continued*

Experiment, Weight, Date	Time of Period	CO_2 per Minute, c.c.	O_2 per Minute, c.c.	Resp. Quot.	Calculated Calories per Hour		Resp. Rate per Minute	Resp. Vol. per Minute, c.c.	Rectal Temperature C. °	Blood Pressure mm. Hg.	Blood CO_2 Combining Power Vol. Per Cent
					Cal.	Per Cent Var.					
XLVIII	11:45	11.8	18.0	0.66	5.04	....	37	366	36.3	108	
2700 gms.	12:12	13.7	18.4	0.74	5.18	....	36	363	36.2	95	
22/7/19	12:35	14.8	18.1	0.82	5.20	....	35	391	36.0	105	
	2:25	11.4	14.5	0.79	4.13	−20	27	395	36.3	60	
	2:49	11.8	13.9	0.85	4.03	−22	26–64	550	36.3	65	
	3:30	17.2	22.3	0.77	6.34	+23	30	424	36.2	130	
	4:02	....	....	....	....	....	40	426	36.2	115	
	4:35	12.7	18.6	0.68	5.23	+ 2	40	524	36.2	100–115	
XLI	11:50	15.9	23.1	0.69	6.47	....	Irregular	599	36.3	145	
3200 gms.	12:15	18.6	25.7	0.72	7.21	+11.5	114–78	956	36.1	110	
8/5/19	2:55	20.9	26.2	0.80	7.50	+ 7.3	78–86	1186	36.3	95	
	3:30	12.2	18.0	0.68	5.04	−28	50–48	775	35.6	50–63	
	3:45	15.0	20.3	0.74	5.73	−18	41	1365	36.2	67	
	4:30	13.3	16.1	0.83	4.64	−33	27	797	35.4	105	
	4:45	12.9	19.3	0.67	5.40	−23	38–34	727	35.3	80–95	

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CHAPTER XI

SOME CHANGES IN BLOOD AND URINE

Already, in previous chapters, accounts have been given of the concentration of the corpuscles in the superficial and deep capillaries and of the reduction of the blood alkali. Other changes in the blood and also typical changes in the urine have been reported in shock cases.[1] Some of these observations, particularly those on the cellular elements of the blood, have been confirmed. Others have been reported only by single groups of observers who have studied relatively few cases. The following data are presented, therefore, to some degree because of their interest and suggestive value rather than because they are to be regarded as well established facts.

Traumatic Leukocytosis.—In 1917 Govaerts (1) noted that after wounds there is a constant leukocytosis which may attain a high degree, that is, from 30,000 to 50,000 white blood corpuscles per cubic millimeter. The increase in the number of white cells occurs early. Figures as high as 25,000 corpuscles have been found an hour and a half after, and 35,000 two hours after, the receipt of the injury. Furthermore, the leukocytosis rapidly diminishes, and within forty-eight hours it usually disappears. In general it is more marked the more serious the wounds. The white corpuscles which are most abundant are of the polynuclear form. The reaction is certainly not of infectious origin, for it may be observed after fractures without rupture of the skin, and, furthermore, the leukocytosis of infections does not occur promptly after injury and does not pass away within forty-eight hours. It is a leukocytosis, therefore, of purely traumatic origin. Govaerts (1, p. 36) points out that leukocytosis is a very early sign of hemorrhage and may be, therefore, of considerable diagnostic interest in case of abdominal contusion, where it may indicate the existence of a vascular lesion and raise the question of an operation (1, p. 362).

[1] Cornioley and Kotzareff (Revue de chirurgie, 1921, 59:233) have reported eosinophilia as a symptom characteristic of muscle-injury shock, both in lower animals subjected to experiment and in human beings suffering from accidental shock.

The statements of Govaerts were partially confirmed by Keith (2), especially in cases of wounds associated with severe primary hemorrhage. On the other hand, in cases of internal wounds involving viscera, even with an associated hemorrhage, he found no striking increase in the white count, the highest in the series being 22,000. Brodin and Saint Girons (3) have repeated almost exactly the observations of Govaerts. They noted a leukocytosis ranging from 15,000 to 70,000 corpuscles per cubic millimeter with a very early appearance of the reaction—45,000 at the end of an hour from the time of being wounded, and 65,000 after four hours and a half. In general the most severely wounded had the highest number of leukocytes. They also found in their fifty cases that leukocytosis was more intense when there was a wound of the thorax, of the abdomen, or of the head than when there were wounds of the limbs, and they attributed the difference to absorption from the contused tissues, independent of infection (3, p. 375). Predominance of large mononuclear cells over combined lymphocytes and small mononuclear forms signify, they state, a grave condition. On the contrary, predominance of the two latter groups over the large mononuclear leukocytes is a favorable sign and more favorable as the predominance is more marked. Hooper, at Béthune, observed during the summer of 1917 a similar leukocytosis in cases of low blood pressure, but his figures have not been published.

In experimental shock, Crile (4) has reported that the leukocytes are decreased, and Mann (5) likewise has found that, in shock produced by intestinal manipulation, there is an enormous decrease of the white cells. The significance of the discrepancy between the clinical and these laboratory observations on the number of leukocytes per cubic millimeter is not yet elucidated.

The Sugar Content of the Blood.—In the course of observations at Béthune, the possibility was taken into consideration that the reduced alkali reserve in shock cases might be due to a "starvation" acidosis. It was suggested by the fact that not infrequently men were brought to the Casualty Clearing Station about noon who had been wounded and shocked in a night raid and who testified to having eaten nothing since the previous afternoon. After being admitted and put to bed they were often too ill to take nourishment. In consequence they might be without food for a period which could be expected to produce metabolic disturbances. A prime condition for "starvation" acidosis is lack of sufficient carbo-

hydrate in the body to play a necessary rôle in the oxidation of fat—under the circumstances the oxidation of body fat—which is being used as a source of energy. Determinations of blood sugar were made in order to show whether or not a deficiency of carbohydrate prevailed. In Table XVI are presented the results of observations on the sugar content of blood in some cases of shock and hemorrhage.

TABLE XVI

SUGAR CONTENT OF BLOOD IN CASES OF SHOCK AND HEMORRHAGE

Initials	CO_2 Capacity Vols. per cent	Blood Sugar	Initials	CO_2 Capacity Vols. per cent	Blood Sugar
A. H. P.	47	0.10	W. G.	47	0.18
F. W.	34	0.11	O. C. R.	50	0.12 (1 hr. after hit)
W. B.	36	0.15	O. C. R.	40	0.15 (6 hrs. aft. hit)
J. B.	42	0.19	A. S.	60	0.12 (before op'n)
H. H.	42	0.22	A. S.	52	0.11 (after op'n)

From these observations it is clear, in the first place, that there is no lack of sugar in the blood; indeed, that the amount is actually above the normal (0.1 per cent). Furthermore, there appears to be no relation between the variations of the carbon dioxid capacity of the blood and the percentages of sugar. In the course of the examination of the blood of animals subjected to shock from muscle injury (see p. 144), Aub and Wu (6) found that after shock was established the blood sugar was considerably increased over the amount previously present. An inference of hyperglycemia in shock cases was drawn by Thannhauser (7), because of discovering sugar in the urine of such cases.

Nitrogen Retention in the Wounded.—By a chemical analysis of the blood of wounded men, Duval and Grigaut (8) determined that, parallel with a diminution of the non-protein nitrogen of traumatized tissues, there was an increase of non-protein nitrogen and of residual nitrogen (that is, total non-protein nitrogen minus urea nitrogen) in the blood. The augmentation of nitrogenous material in the blood was related to the intensity of phenomena of toxemia in the individual. For the majority of the wounded (8,

p. 874) it was slight, it started promptly after the wounding, was at its height on the second day, and gradually returned to normal. Only rarely were the values double the normal (8, p. 875). In cases of secondary shock the figures for non-protein and residual nitrogen were generally much higher and in the plasma amounted to approximately double the normal. In Table XVII are presented their average findings in centigrams per thousand grams of material (8, p. 876).

TABLE XVII

BLOOD NITROGEN IN SHOCK

	Normal	Wounded Without Shock	Wounded With Shock
Non-protein Nitrogen			
Plasma	23	29	43.1
Total blood	32	36.5	58.0
Blood cells	48	57	65.8
Residual Nitrogen (Non-protein minus Urea)			
Plasma	10	12.6	20.9
Total blood	20	19.1	32.4
Blood cells	32	37.4	44.9
Urea			
Plasma	..	16.7	22.8
Total blood	..	17.3	26.12
Blood cells	..	18.8	21.05

Duval and Grigaut noted that, as the wounded recovered, the curve of excessive blood nitrogen was reduced, but that if conditions led to death, there was a gradual rise. The increase of non-protein nitrogen in the blood of shock cases suggests the increased nitrogen of nephritis, and the low blood pressure with consequent diminution of kidney activity might be invoked to account for the accumulation in the blood stream. In nephritis, however, the nitrogen which accumulates is, in the main, urea. As Table XVII shows, however, the retention in cases of shock is to a very large degree residual nitrogen.

In a study of the blood of animals shocked by injury to muscles, Aub and Wu likewise found an increase of the nitrogen in the blood,

roughly inverse to the reduction of metabolism. Both urea and total nonprotein nitrogen were augmented. Of the latter, the constituent most conspicuously high in amount was creatinin, which was increased much more, proportionately, than the urea. This change was interpreted as indicating autolysis of the damaged muscular tissue, and as pointing perhaps to the presence of other undetermined protein substances.

Duval and Grigaut associated their observations with those of Nanta, who discovered that in the severely wounded there were histological changes in the liver (8, p. 881). They suggest that the hepatic injury is possibly due to a poisonous action of nitrogenous substance liberated by the traumatism.

Changes in Urinary Constituents.—Wertheimer, Fabre and Clogne (9) made analysis of the urine of ten severely wounded men who were suffering from shock and found an increase of the apparent acidity and also of the ammonia content. Determination of the apparent acidity gave figures equivalent to between 1.46 g. and 3.64 g. of hydrochloric acid for the twenty-four-hour amount. The average was 2.65 g., which should be compared with the normal 1.80 g. This hyperacidity was accompanied by an increase in urinary ammonia, the figures for which varied between 0.75 g. and 2.4 g. The average was 1.36 g., instead of the normal 0.75.

The amount of urea, sometimes low in urine obtained by sound at the time of arrival, increased in later samples, in spite of the shock. The average of elimination in the first twenty-four hours was 33.50 g.

They also state that acetone bodies were present in the urine of these cases, as well as in severely wounded men who were not suffering from shock. In the latter group the acetone bodies amounted to 40 mgm., whereas in the shock cases the average for the acetone bodies was 106 mgm.

When there was recovery from the wounds, a diminution of the apparent acidity occurred as well as a diminution of the acetone bodies, but the amount of ammonia and urea remained high. The elimination of urea continued for some time at a high level, reaching for the twenty-four hours, 40 and even 57 g.

In connection with the increase of residual nitrogen in the blood of shocked men, the discovery by Mestrezat (10) is of interest. He observed that in the urine of such cases the undetermined nitrogen was particularly high.

Interpretation of the foregoing observations on changes in the blood and urine is still difficult. There is clearly a disturbance of metabolism, which is possibly associated with an alteration of hepatic function. On the other hand, as will be shown later (see p. 154), there is evidence of nitrogenous material being given off from injured tissues, which may account in part for the changes observed both in the blood and in the urine. The results are suggestive for further work on the metabolism in shock.

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CHAPTER XII

COLD, SWEATING AND THIRST

It has been a common observation that patients suffering from shock have characteristically a low temperature. The skin feels cold, and the thermometer registers below normal. Weil (1) has recorded cases of wounded men whose temperatures ranged between 91.4° and 95° F. and he reports two cases in which the temperature was respectively 87.8° and 88.8° F. In the former, there was a severe grenade wound of the foot, and in the latter the foot had been blown off and there had been much loss of blood. Among the wounded who were studied at Béthune, the temperature on admission was usually low, but I have never seen it below 95° F. by mouth.

The cold state observable on the skin of the legs and arms is not wholly superficial. In the course of operating on cases of shock it was possible to apply sterile thermometers to the deep tissues as they were exposed and these were found likewise to be cold.

The Relation of External Temperature to Shock.—That the incidence and severity of shock are in some way related to the coldness of the surroundings of the wounded man seems well established. Members of shock teams working in the A. E. F. during the summer and fall of 1918 reported the strikingly larger number and the greater severity of the cases of shock in the cold, wet months of the fall, September and October, as contrasted with the cases seen during the fighting in the warm weather of July and August. Similar observations have been made by Weil (1) who has emphasized especially the influence of rain in combination with cold. In wounded men he noted that subnormal temperatures were not so extreme in February, for example, as they were in the rainy periods of December and March.

The reverse aspect of the relation of shock to external tempera-

ture is seen when heat is applied to the patient. Nothing is more striking than the improvement which often occurs when a wounded man, cold, wet, and apparently half dead, is brought to a hospital and warmed. I recall one such case in which at the time of admission there was no pulse palpable at the wrist and the condition of shock seemed to be thoroughly established. On his being warmed, however, for only 45 minutes, the pulse was restored in good volume and the arterial pressure was found to be approximately 110 mm. Hg. There is universally favorable testimony regarding the great efficacy of heat as a restorative for shocked men. Wallace (2), whose experience with shock cases during the War was very extensive, has written, "All the established methods of treatment were used, but warmth combined with rest greatly outstripped all others in favour." In French forward hospitals, the place where shock cases were treated was marked by the sign, "Salle de Réchauffement."

It appears clearly from clinical observations, therefore, that a low body temperature is typical of shock and in all probability is favorable to the further development of shock; and, on the other hand, that the raising of a subnormal temperature to normal is associated with improvement of the patient.

Conditions Conducive to Low Body Temperature.—The normal temperature of the body is the result of an equilibrium between heat production and heat loss. The circumstances which prevail in shock are such as to affect both processes.

As shown in a previous chapter, a reduction of the blood pressure below the critical level of 75 mm. Hg. checks the rate of metabolic processes in the body. The heat production in calories may fall to only 67 per cent of the normal. The natural reaction of the organism when there is a tendency towards subnormal temperature is to produce more heat by shivering or by engaging in vigorous muscular activity. The former reaction is seldom seen in wounded men. I have recorded shivering in one instance, but as a rule, in my experience, the sufferer from shock does not exhibit this natural response to cold. Furthermore, the nature of the wound usually precludes any possibility of muscular effort which would supply extra body heat. The general and the special arrangements for compensatory heat production, therefore, are no longer efficient when shock is established. Indeed, as already shown, the routine basal heat production may be much reduced below normal. For

these reasons alone, therefore, the low temperature of shock might reasonably be expected.

The body temperature may be low, also, because of conditions favorable to rapid loss of heat. Cowell (3) has called attention to one of the most readily notable phenomena accompanying severe wounds—profuse sweating. He has reported that wounded men sometimes complain more of the sweating than of the wound itself. The same phenomenon may be observed when shock appears in the course of operation. I have seen the depressions about the eyes fill with sweat several times in the course of an operation during which shock was developing. It seems possible that the sweating is a response of the sympathetic system as a whole to the fall of blood pressure, a response which involves not only vasoconstriction but also stimulation of the sweat glands. The appearance of sweating after profuse hemorrhage might be similarly accounted for. Of course the phenomenon differentiates shock as seen in man from the experimental shock of lower animals, in which the sweat glands are absent or relatively inactive. Sweat represents fluid permanently lost from the body—in lower animals this may not occur.

Whatever may be the cause of the sweating, it has the effect of augmenting the loss of heat from the body. The most effective normal mechanism for promoting heat loss is the evaporation of sweat from the skin. When the wounded man sweats, therefore, he is subjected to the same physical process that occurs when the working man sweats, that is, his store of heat is reduced. Still another way in which sweating favors heat loss is through a wetting of the clothes. Clothing keeps us warm by holding enmeshed about the body a layer of air. If the air is replaced by water, a poor conductor of heat is replaced by a fairly good conductor. Then, if the surrounding atmosphere, or the surface on which the patient lies, is colder than he is, heat will pass away from him more rapidly than if his clothes were dry.

The conditions just mentioned are especially favorable to heat loss from men wounded in battle. Attacks are commonly made at the break of dawn or somewhat earlier. This is the coldest part of the day and the ground is likely to be both cold and wet. When a man is severely wounded, he falls. Then all of the factors which have been detailed above begin to operate to reduce his store of body heat. If the blood pressure is promptly reduced by hem-

orrhage, the heat production decreases, and simultaneously sweating with consequent loss of heat by evaporation and conduction sets in. Thus, in so far as cold is a factor favorable to the development of shock, the processes occurring after a severe wound are all operating to induce the shock state. Of course, if the attack is being made in cold wet weather, the conditions leading to a loss of body heat are even more effective.

The Effects of Cold in the Body.—The precise way in which a low temperature favors the development of shock is unknown. We are aware that a reduction of temperature is accompanied by a retarda-

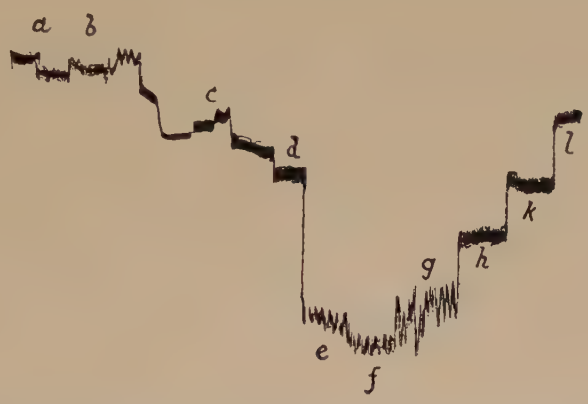

FIG. 10.—COOLING WITH RECOVERY. CAT UNDER URETHANE. (*a*) Commenced cooling, Temp. 35.8°. (*b*) Temp. 34°. Shivering. (*c*) 1.25 hours later. Temp. 30.8°. (*d*) After another hour. Temp. 28°. Pulse 128. Resp. 32. (*e*) Forty minutes later. Temp. 25°. Pulse 64. Resp. 10. Apparently heart block. Muscles lax, no shivering.. (*f*) Began to warm. (*g*) Shivering. Temp. 26°. Pulse 106. Resp. 20. (*h*) Half-an-hour after *f*, Temp. 27°. (*k*) Seven minutes later. Temp. 28°. Pulse 130. Resp. 28. General shivering. (*l*) Seventeen minutes later. Temp. 30°. Pulse 140. Resp. 36.

tion of the rate of chemical change in bodily organs. Whether this fact, however, is connected with the incidence of shock is not yet determined.

Mann (4) and also Seelig and Lyon (5) have reported that the experimental application of cold to the abdominal viscera results in the development of a shock blood pressure. Because of the clinical testimony that a relation exists between cold and the occurrence of shock, Bayliss and I (6) undertook some further experiments with the hope of analyzing the relationship. We found that blood pressure could, indeed, be greatly reduced by cooling an animal to 25° C. (77° F.) (see Fig. 10). This effect, however,

was chiefly due to slowing of the heart beat, the pressure falling with the rate. When the animal was warmed there might be complete recovery of the normal pressure. On the other hand, probably some additional effect is produced besides that on the heart, for, after slight hemorrhage, cooling resulted in a fall of pressure which was not restored when the animal was warmed.

An action of cold which may be favorable to reduction of the volume of circulating blood is that of causing stagnation of corpuscles in the capillaries. It is known that blood drawn from a cold finger contains a larger number of corpuscles in a given volume than that drawn from the same finger after it has been warmed (7). Hough and Ballantyne (8) noted that exposure of the hand to cold caused a rise of capillary pressure accompanied by an almost complete disappearance of the veins. The hand, at first red, later became more or less cyanotic, indicating a stagnation of blood in the capillaries. Although the infrequency of cyanosis in shock cases indicates that a large accumulation of blood in surface capillaries rarely occurs, it seems probable that cold, by causing constriction of the venules, augments other processes, such as a low head of arterial pressure, in promoting stagnation of corpuscles in capillary areas (see p. 46).

Another way in which cold might affect the circulatory flow, especially through the capillaries, is by altering the viscosity of the blood. Denning and Watson (9) found that the viscosity was increased 3 per cent with a fall of 1° C., and that the temperature factor was more effective the larger the number of corpuscles present. Thus the coldness of the skin and deep tissues in the limbs, together with the increased concentration of the corpuscles in the capillaries, and the contraction of the venules, would all be favorable to the segregation of a considerable amount of blood in capillary areas. For the present this explanation seems the most reasonable one to account for the observation that chilling is a factor favorable to a fall of arterial pressure and that warming may cause the pressure to rise again.

Sweating and Thirst.—Previous analysis has revealed that one of the prime factors in causing low blood pressure in shock is a reduction of blood volume. It is of the utmost importance that there should not be any greater loss of fluid from the body under such circumstances than is absolutely necessary,—as, for example, that associated with keeping moist the respiratory surfaces. Never-

theless, as we have just seen, shock is likely to be accompanied by a very considerable passage of water through the skin in the form of sweat. This fluid, which is a salt solution, is permanently lost so far as any service in restoring blood volume is concerned.

As I have pointed out elsewhere (10), a diminution of the water content of the body is accompanied by lessened activity of the salivary glands and a consequent experience of thirst. Bayliss and Jonescu (11) have shown that lack of oxygen due to deficiency in the air breathed, or to low blood pressure from hemorrhage, causes a rapid decrease in the rate of salivary secretion. Thus, sweating, hemorrhage and low blood pressure would coöperate in causing thirst. The natural effect of thirst would be the taking of water, which, of course, would increase blood volume (see p. 177) and, by raising blood pressure, would again restore the normal functioning of the salivary glands. No feature of a shock ward after battle is more impressive than the universal demand for water. When the wounded are capable of retaining it without vomiting they will drink astonishing amounts. In one such case at Béthune I recall giving a man water repeatedly and frequently as he called for it, and in spite of these attentions he declared, "I want to keep drinking all the time."

Unfortunately patients who are suffering from shock are commonly unable to retain anything given by stomach and will promptly vomit the fluid which they drink. The complex of sweating which takes much needed water away from the body, and vomiting which prevents restoration of water to the body, is one of the most distressing difficulties in the care of shock cases.

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CHAPTER XIII

THE DAMAGE DUE TO PERSISTENT LOW BLOOD PRESSURE

In tracing the secondary effects of a low blood pressure, we have seen that when the pressure falls below a critical level there is a reduction of the alkali in the blood, a slower rate of metabolism, and with the lessened heat production a lower temperature. Suggestions have been made repeatedly in the course of previous discussion that these results are the natural consequence of insufficient delivery of oxygen to the tissues, because of a greatly diminished volume-flow of blood. Support for the view that there is, in shock, a want of oxygen is found in certain similarities between the symptoms of shock and the symptoms observed at high altitudes, or in association with carbon monoxid poisoning. In both these latter conditions, just as in shock, characteristic features are nausea, vomiting and faintness (1).

Varying Sensitiveness of Tissues to Want of Oxygen.—In an extensive series of studies, Pike, Guthrie and Stewart have examined the capacity of different tissues of the body to function after having been totally deprived of their blood supply for varying periods. In general it may be stated that muscles and glands reveal a remarkable endurance of anemia without serious damage (2). The muscles will withstand this injurious condition much longer than the nervous system, for example. The same may be said of glandular structures.

The most sensitive cells in the body are found in the brain, but a remarkable gradation of resistance to anemia is found in different neurons. Most sensitive of all are cells of the cerebellum and cerebrum. Mayer (3), Batelli (4), and also Stewart, Guthrie, Burns and Pike (5) have offered concordant evidence that after 15 minutes of anemia, restoration of cerebral function is no longer constant. Gomez and Pike (6) on examining the effects in detail observed that the small pyramidal cells of the cortex are especially sensitive—8 minutes of anemia killed many of them; and that the

Purkinje cells were next in order—13 minutes producing chromatolysis in them.

The cells of the medulla are more resistant. Gomez and Pike found that anemia for 8 to 13 minutes produces in them only slight lesions or no changes at all, and that anemia should last for 20 or 30 minutes in order to produce alterations incompatible with complete recovery. The cells of the spinal cord apparently withstand a lack of blood flow for a somewhat longer period than those of the bulb; different observers have reported paralysis or recovery after shutting off the blood supply from 45 to 60 minutes (7). The outlying ganglia of the sympathetic chain, according to Schröder (8), are even less delicate, for they can be completely deprived of blood supply for an hour and will then function if supplied with blood. And Burket and I (9) showed that the nerve cells of the myenteric plexus will endure anemia for as long as 3 hours without showing either loss of function, or change or disappearance of structure. From this evidence it is clear that in the nervous system there is a hierarchy of cells with varying ability to meet the circumstances of insufficient oxygen supply.

In shock, of course, there is not a total absence of oxygen delivery to the tissues, as in the experiments reported in the foregoing paragraphs. On the other hand, the indications are definite that, even with the blood flowing, conduction in the nervous system may be completely checked when the oxygen supply becomes insufficient. In some experiments, performed in the Harvard Physiological Laboratory by E. L. Porter (10), on variations in the irritability of a reflex arc under asphyxial conditions, it was discovered that when the oxygen supply is diminished and accumulation of carbon dioxid in the blood is prevented, the reflex abruptly disappears when the oxygen content of the arterial blood is reduced on the average to 4.5 volumes per cent. Lack of oxygen proved to be much more important than accumulation of carbon dioxid in abolishing the capacity to transmit nerve impulses (10, p. 231).

Evidence of Damage to the Central Nervous System from Low Blood Pressure.—The testimony that insufficient blood supply injures the elements of the central nervous system is both morphological and functional.

Morphological changes as a consequence of diminished blood flow have been reported by Dolley (11), who found that after repeated hemorrhage, the Purkinje cells of the cerebellum under-

went a sequence of alterations exactly identical with those observed in shocked animals. Mott (12) has reported studies of the cell changes in cases of shock in which for some hours before death there was low blood pressure, and has found that there is general chromatolysis, a change which he attributes to the prolonged anoxemia. Besides the chromatolysis, Mott noted that many of the cells of the medulla and also some of the Purkinje cells show a tendency to profuse purple staining when a double stain such as a basic blue and eosin dye is used. This alteration in the staining reaction denotes a biochemical change, possibly different in character from that associated with the diffusion of the Nissl substance.

The functional evidence of injury to the nervous system from low blood pressure has come mainly from examination of disturbances in vascular reflexes during the development of shock. As previously noted (see p. 18) W. T. Porter and his collaborators proved that after a prolonged low blood pressure in shocked animals stimulation of afferent nerves could cause either a rise or a fall of blood pressure. They concluded, therefore, that even in extreme shock the vasomotor center is still active. It was not, however, until perfusion experiments were performed on peripheral vessels still connected with the vasomotor center that direct proof was obtained showing whether the center was over-active or under-active. Such perfusion experiments, conducted by Erlanger, Gesell and Gasser (13), and more recently by Cattell (see p. 20), have demonstrated that although in the early stage of shock, whether due to abdominal injury or to crushing of muscle, the vasomotor tone is increased, in the later stages there is practically invariably diminished tone and lessened peripheral resistance. The tendency of the vasomotor center, when the blood pressure becomes low, is to compensate by increased activity. The failure of the center to respond thus to the stimulus of a low pressure in the late stages of shock must be regarded, therefore, as signifying that the center has become injured to such a degree that it is incapable of responding.

Bayliss (14) has pointed out that the vasomotor center is not alone among the bulbar centers in suffering from low blood pressure and the consequent sluggish blood flow. He noted that when the average blood pressure remained below 58 mm. Hg. in cats, not only were vasomotor reflexes abolished but the rate of respiration fell to 6 or less per minute. Various other experiments showed

that when the blood pressure was less than 70 mm. Hg., from one and a half to two hours, more or less, a paralysis of the bulbar centers would occur. The respiratory center in the cat appears to suffer before the vasomotor center, though it may continue to discharge at the slow and ineffective rate of 3 or 4 per minute when the vasomotor center has lost its excitability. Bayliss suggests that different animals probably behave differently as regards the order in which their vital centers fail and that in man the vasomotor center may begin to lose its functional stability before the respiratory center.

In order to secure evidence as to the progressive nature of the

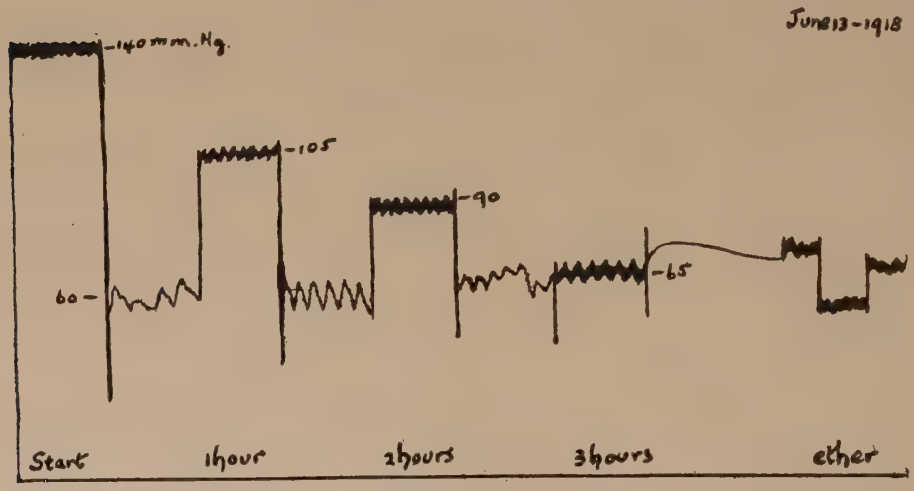

FIG. 11.—GRADUAL FAILURE OF THE BLOOD PRESSURE TO RISE. The pressure is held at 60 millimeters of mercury for successive periods of one hour and then released for five-minute intervals.

damage done to the nervous control of the circulation in consequence of an insufficient blood flow, Cattell and I made observations on the effects of reducing the blood pressure to 60 mm. Hg. for varying times by the method of intrapericardial compression of the heart (see p. 64). When the pressure had been thus reduced to that level it was held there for an hour. The compression of the heart was then released by lowering the fluid column. Usually when this is done the blood pressure will be restored completely, or nearly completely, to its normal level (see Fig. 11). If now the pressure is again lowered to 60 mm. and held there for an hour it does not rise so high and when held to this low level for another hour it may not rise at all.

It might be supposed that the failure of the pressure to rise after being held persistently low for 3 hours would be due to a loss of blood volume by escape of plasma into the tissues through more permeable capillary walls. Observations with the hematocrit in these cases, however, suggest that this was not an important factor. In Table XVIII are the average hematocrit readings when the pressure was reduced to different levels and held there for periods of one, two and three hours. As the figures clearly show, the percentage of corpuscles gradually fell, indicating that there was a dilution rather than a concentration of the arterial blood.

TABLE XVIII

CHANGES IN THE COMPOSITION OF THE BLOOD CAUSED BY REDUCING BLOOD PRESSURE

Number of Cases	Pressure Reduced to	Average Hematocrit Readings (Percentage of Corpuscles)			
		At Start	1 Hour	2 Hours	3 Hours
4	70 mm. Hg.....	47	46	46	47
12	60 "	40	37	31	27
4	50 "	38.5	34.5	26	26

The explanation which appears most reasonable to account for the failure of the pressure to rise after persistence at the low level is that the nervous agencies which control the circulation have suffered damage—a damage due to inadequacy of the circulation itself. The reasonableness of the conclusion is supported by the observed relaxation of vascular tone in late shock (see p. 20), and by tests of the responsiveness of the vasomotor center to stimulation by asphyxia. As shown in Fig. 13 (p. 145), at an early stage in shock there may be an asphyxial rise of pressure, and later, though the heart still beats and respiration is still active, the asphyxial rise does not occur, that is, the vasomotor cells are no longer excited by the blood changes. LaCroix (15) has noted that in cases of shock after severe wounds there may be total immobility of the pupil no matter how intense the light. This failure of the pupillary reaction points to a block of the nerve impulses along the reflex path involved in

the reaction and is further indication of injury to the nervous elements.

The Importance of the Time Factor in the Development of Shock.—Experiments cited above have definitely proved that with an acute lack of oxygen, nerve cells abruptly cease to function. The loss of consciousness when one faints is a common example of the extreme dependence of nervous elements on continuous oxygen supply. The experimental and clinical observations on the effects of prolonged low pressure point to the fact that these sensitive cells may be gradually harmed if, instead of acute anemia, there is prolonged partial anemia.

The gradually damaging effect of persistent low blood pressure is of the utmost importance both in understanding and in treating shock. When the vasomotor center has lost its capacity to maintain vascular tone there is no known remedial agent which can be applied to bring the blood flow back to its normal condition. If the medulla is destroyed in an animal, the blood pressure falls to approximately 40 mm. Hg. and there remains. Intravenous injections of blood or other fluid will raise the pressure only for a few moments. An incredible amount of fluid may thus be introduced into the vessels without any lasting rise of pressure. When a man has been for a long time in a state of shock, so that the vasomotor center fails to hold the blood vessels in a state of moderate contraction, he reacts much as the experimental animal does with the bulbar center destroyed. Transfusion leads to no permanent gain—the beneficial effect is fleeting. When that stage has been reached, the secondary harm from insufficient oxygen has been too great to permit resuscitation.

The foregoing considerations emphasize the prime importance of early treatment of the low blood pressure of shock. As Pike and Coombs (16) have stated, injured nerve cells require a better blood supply for their restoration than uninjured nerve cells do for their maintenance. Therefore, if the blood pressure has fallen below a critical level of approximately 80 mm. Hg., and has shown no evidence of rising, it is desirable that it be raised to 120 mm. Hg., if possible, in order to provide the most favorable conditions for repair of the damage which has been done.

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CHAPTER XIV

SENSITIVENESS TO ETHER AND CHLOROFORM CONTRASTED WITH NITROUS OXID AND OXYGEN

That patients suffering from traumatic shock are markedly sensitive to operative procedures has long been recognized. This sensitiveness has led surgeons to hesitate and to defer operation in shock cases because of the danger of intensifying rather than improving the condition. When the surgeon interferes there may be an alarming augmentation of the shock state—a sharp fall of blood pressure or utter collapse. It becomes a matter of great importance, therefore, to learn whether any *avoidable* elements in the complex of a surgical procedure are reducing the patient's chances.

In the course of an operation there are three elements which may be considered as capable of inducing collapse: the surgical procedure itself, hemorrhage, and the anesthetic. Obviously, if circumstances require the operation, it is impossible to avoid the use of surgical methods. It is also clear that hemorrhage may play an important part in causing a collapse. As previously pointed out (see p. 11), after blood pressure has been restored by excessive action of the vasoconstrictor center, a slight further hemorrhage may turn the scale and lead to pronounced fall of pressure—"critical further bleeding" may occur during the operation and thus lessen the probability of recovery. With reference to the third factor, the anesthetic, the testimony obtained during the World War has been highly significant.

Effects of Chloroform and Ether in Shock Cases.—In 1917 Captain Geoffrey Marshall (1), a careful observer, who had had large experience as an anesthetist at a casualty clearing station in the Flanders sector of the British line and who had kept careful records of the blood-pressure changes in his cases, reported on the effects of anesthetics in different types of the wounded. Chloroform he sharply denounced as an anesthetic in shock cases. "If chloroform be used," he remarks, "the patient is likely to die on the table." In Marshall's experience, ether may improve the condition of the

shocked man during the operation, but is likely to be followed by a collapse an hour or two afterwards.

The observations made at Béthune brought out strikingly the fact that, in cases of shock, the fall of blood pressure under ether anesthesia may be calamitous during the course of operation. In Table XIX are presented records of five illustrative cases which show the blood pressure both before and after operation, together with the reduction of the alkali reserve as measured by the decreased carbon dioxid capacity of the blood plasma. In these cases, the average fall of blood pressure was from 92 systolic, 68 diastolic,

TABLE XIX

CHANGES OCCURRING IN THE COURSE OF OPERATION

Initials	Duration of Operation Mins.	CO_2 Capacity Vols. per cent		Blood Pressure mm. Hg.	
		Before Operation Per Cent	After Operation Per Cent	Before Operation	After Operation
S. R.	75	58	46	82–58	58–36
B. S.	40	58	46	88–62	74–42
F. A. T.	60	56	40	98–80	64–48
G. J. H. H.	45	50	44	90–62	64–46
J. H. C.	45	47	40	102–80	50–28
Averages.....	53	54	43	92–68	62–40

to 62 systolic, 40 diastolic, in other words, the systolic pressure at the end of operation might be well below the diastolic pressure at the start. This ominous sinking of the blood pressure was repeatedly observed during operation on shock cases.

In general, it was noted that the cases in which the alkali reserve was most decreased were more likely to suffer a greater fall of arterial pressure than those in which there was a normal alkali content of the blood. At the time these observations were made it was felt that possibly the lower alkali content itself was conducive to rendering the patient more sensitive to operative procedures, and there is experimental evidence that this is true, as will be shown later. The important matter to be emphasized now, how-

ever, is that in the course of operations on shock cases the blood pressure may suffer quite as sharp and dangerous a fall as occurs in consequence of hemorrhage, and that this may happen whether chloroform or ether is used as an anesthetic. In the cases observed at Béthune, ether was given by the Shipway apparatus, so that warm vapor was delivered to the patient. Furthermore, in order to make sure that the reduction of the alkali reserve was not due to an insufficient percentage of oxygen in the lungs, the ether vapor was in some instances driven through the apparatus by means of oxygen. Patients treated in this way reacted quite as badly as did others for whom air was employed to carry the ether.

Although the observations of Crile and Menten (2), Austin and Jonas (3), Morriss (4), Caldwell and Cleveland (5), and others have shown that there is regularly some diminution of the alkali reserve of the blood in the course of a surgical operation, the very striking fall which is seen in such cases, as illustrated in Table XIX, may be largely accounted for by the sharp drop of the head of pressure in the arteries. The question that needs to be considered, therefore, is the essential one as to why the pressure falls.

Observations on Ether Sensitiveness in Experimental Shock.—Although clinical results pointed strongly to the anesthetic as the agent causing the further fall of blood pressure during operation, it was not until that factor alone was tested under experimental conditions that the evidence became quite clear. The Béthune observations showed that the lower the alkali reserve, the more sensitive the individual to operative procedure. The suggestion thus offered was tested by Dale and Richards (6), who found that if the reserve was experimentally reduced in the dog by injection of acid, the animal became very sensitive to the action of ether, an observation which was confirmed by Bayliss (7). Later, in the course of experiments at Dijon, Cattell and I noted that any condition that deeply disturbed the organism, such as severe hemorrhage or prolonged low blood pressure, was associated typically with increased ether sensitiveness—a marked fall of blood pressure, sometimes 40 or 50 mm. Hg., occurring when ether was administered until the wink reflex disappeared (see Fig. 12).

As previous discussion has shown (see p. 15) the blood pressure may fall because of (*a*) decreased blood volume, (*b*) diminished output from the heart, or (*c*) depression of vasoconstrictor tone. That the fall of pressure during operation on shock cases is due wholly

to decreased blood volume is improbable because the fall may occur too rapidly to permit a sufficient loss of fluid to account for the drop. There remain, consequently, the heart and the vasomotor center to be considered. Are there effects of ether on either of these factors which would account for the baneful results of operative interference? This is a question which was first investigated experimentally by Lieutenant Cattell at Béthune and later brought to more complete analysis in studies at the Harvard Physiological Laboratory.

The Effect of Ether on the Heart.—Du Play and Hallion (8), in the course of investigations on changes of blood pressure under ether and chloroform anesthesia, made use of alterations of the volume of the isolated kidney to register circulatory effects. They concluded that the first rise in the blood pressure curve was due to vasoconstriction and that the subsequent fall was the consequence of decreased activity of the heart. Because ether was less depressant to the heart, the blood pressure was higher under this anesthetic than under chloroform. Cushny (9) found that ether may cause the blood pressure to fall, probably due to a depression of the heart, but that this may be compensated for by reflex vasoconstriction.

These observations were confirmed by Cattell, who noted that in a normal unshocked animal the first effect of ether in high concentration in the inspired air is a rapid fall of blood pressure. This fall is quite temporary, however, for the low pressure is followed promptly by a rise to the normal level while the ether is still being administered. By measuring the heart volume, Cattell found that from the very beginning of the administration of ether there is a loss of tone in cardiac muscle as shown by increased cardiac volume and decreased contraction, and that the tone becomes less and less as anesthesia deepens, until a maximum tonelessness is reached at the death of the animal. Studies on the isolated auricle of the turtle's heart revealed that ether, when present in such concentration as occurs in blood under ordinary anesthesia, produces a a marked decrease of tone and extent of contraction. It appears proved, therefore, that of the two elements, the heart and the vasoconstrictor center, the heart at least suffers depression in consequence of ether anesthesia.

The Effect of Ether on the Vasoconstrictor Center.—The literature regarding the effect of ether and chloroform on vasoconstrictor

tone is so extensive that it will be impossible to review it here. The experimental evidence strongly favors the view that both anesthetics cause, normally, an increased vasoconstriction. Further evidence of this point was obtained by Cattell, who made plethysmograph studies of the hind leg under experimental conditions and found uniformly a decrease in volume during the inhalation of ether. Furthermore, by determining the perfusion time of a fluid introduced into the blood vessels of the hind leg he discovered a marked slowing of the rate under ether, that is, the vessels were more constricted. Still more evidence was obtained by noting the effects of injecting directly into the circulation a saturated solution of ether in normal saline. When the injection was made into an artery towards the head, so that the ether affected first the bulbar centers, there resulted a rise in arterial pressure; on the other hand, when the injection was made into a vein towards the heart, so that cardiac muscle was primarily affected, there was a fall in pressure.

It is important to note that in Cattell's experiments ether caused *no increased constriction of the peripheral arterioles in shock cases.* In severe shock, the administration of ether, therefore, is not associated with greater activity of the vasoconstrictor center. Under such circumstances, likewise, the normal reactions of this center to asphyxia or strong sensory stimulation become less or are entirely absent. Thus, the damage occasioned by low blood pressure, which was considered in the foregoing chapter, is such as to destroy or greatly lessen the capacity of this mechanism to protect the body from a further lowering of the pressure from any cause.

Explanation of the Effect of Ether in Shock.—Cattell's observations suggest an explanation for the depressive action of ether in cases of shock. As shown by the experiments cited above, even in the normal animal the immediate effect of ether is a depression of the heart. Thus the primary fall of blood pressure, when ether is rapidly applied, would be accounted for. Under normal conditions this decreased cardiac action, with its attendant smaller output of blood from the heart, is soon compensated for by reflex peripheral constriction and probably also by direct stimulation of the vasoconstrictor center by the ether in the blood. Therefore, normally, the pressure returns to the usual level, where it remains if the concentration of ether vapor in the blood does not become extreme. In late shock, on the other hand, while ether leads to a similar depression of the heart, there is such impairment of the

natural vasomotor reactions that the compensatory constriction fails to occur. The fall of blood pressure is the necessary result.

Although the failure of the vasoconstrictor center to compensate for low blood pressure, especially in the late stages of shock, is probably due to a lack of capacity to respond to the usual stimuli, there is another explanation which should be kept in mind. There may already exist, in consequence of excessive action of the center, maximum contraction of the arterioles (see p. 20). In that case there would be no possibility of further increase of vascular constriction to compensate for a lessened output from the heart. The depressive action of ether which may be seen immediately after severe hemorrhage is best explained on this latter assumption. In all probability the ether depression which may occur in the early stages of shock, when the vasoconstrictor center is overactive, is likewise accounted for in this way.

Lack of Sensitiveness to Nitrous Oxid and Oxygen Anesthesia.—Although Marshall (1, p. 26) reported serious consequences from the use of ether and chloroform in shock cases, he found, when nitrous-oxid-oxygen anesthesia was employed, that blood pressure might not undergo further fall and that the clinical condition of the patient at the end of operation and thereafter was much more satisfactory than with other anesthetics. Previous to Marshall's testimony, and as a consequence of extensive experience in civil cases, Crile and Lower (10) testified that nitrous-oxid-oxygen anesthesia is less likely to increase shock than is ether. That this anesthetic does not preclude a fall of blood pressure was shown by some observations at Béthune. In one instance during an operation lasting an hour, the blood pressure fell from 76—36 to 68—28 mm. Hg., and in another instance when the operation lasted fifty minutes the pressure fell from 84—60 to 58—36. No explanation was at hand at that time to account for the unusual result in these cases. It seemed probable, however, that at some stage during the operation insufficient oxygen was given.

That the suggestion just made may account for the fall of blood pressure in nitrous-oxid-oxygen anesthesia was indicated by further experiments performed by Cattell at Dijon. He discovered that if nitrous oxid is used in the ratio of six parts to one of oxygen, until the wink reflex disappears, there will be as great a fall of blood pressure as that accompanying ether anesthesia to the same degree. This is true also for nitrous oxid in the ratio of five or four parts

to one of oxygen. On the other hand, if used in the ratio of three to one, a shocked animal may be anesthetized until the wink reflex disappears and the blood pressure will not fall at all. These facts are brought out in the record reproduced in Fig. 12.

The explanation of the difference between nitrous oxid and oxygen, on the one hand, and such anesthetics as ether and chloroform on the other, in their effects on the blood pressure in shock, has not been fully accounted for. The practical matter, however,

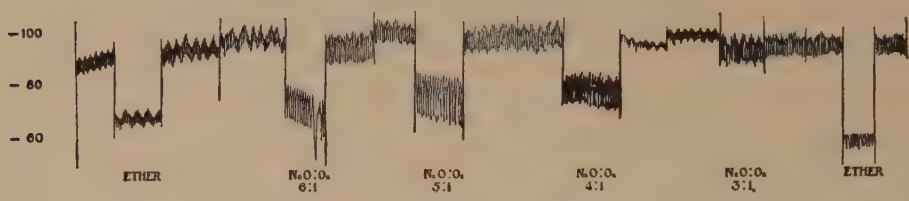

FIG. 12.—RECORD SHOWING EFFECTS OF ETHER AND OF DIFFERENT RATIOS OF NITROUS OXID AND OXYGEN IN A SHOCKED ANIMAL, WHEN THE ANESTHESIA, IN EACH TEST, WAS GIVEN UNTIL THE WINK REFLEX WAS JUST ABOLISHED. Ether and all ratios of nitrous oxid and oxygen above 3 : 1 caused the blood pressure to fall.

is that the patient in shock may be anesthetized with nitrous oxid and oxygen and suffer no appreciable drop in blood pressure, whereas with ether or chloroform the drop is likely to be considerable and possibly highly dangerous.

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CHAPTER XV

DISCUSSION OF THEORIES OF SHOCK

Thus far, in our consideration of shock, we have passed in review the facts of observation as they have been determined in the study of shocked individuals, and as they have been accounted for by experimental testing of suggested explanations. In the main we have been examining the immediate causes of the low blood pressure of shock and the secondary effects which follow from a diminished volume-flow. An explanation for the development of a low blood pressure, apart from hemorrhage, has not been offered. It is at this point that most diverse opinions arise. Many theories have been offered, often with experimental support, to account for the development of low blood pressure. Commonly in treatises on shock such theories are given first place. I have purposely deferred a presentation of them because it seemed to me important to have in mind the facts which have recently been discovered and thus to be able to test the theories by the facts which must be accounted for. As we proceed we shall come upon new facts that have not hitherto been mentioned; these will take their place with others in determining the adequacy of any theory which is suggested.

The Importance of Theories.—A theory of shock not only has the values which a theory of any other obscure state may have, in concisely systematizing and rationalizing our comprehension of a complex group of phenomena, and in making clear where knowledge is lacking and thus suggesting lines of further work; it is also likely to have a direct application to practice. For example, the acapnia theory of shock, which is based on the belief that by reduction of the CO_2 of the blood harmful, shock-producing conditions arise in the body, involves as a practical mode of treatment rebreathing the expired air or breathing an excess of CO_2 in order to restore to the body what is lacking. Or again, the view that shock is of toxic origin suggests as a practical consequence that a prime element in treatment is removal of the focus in which the toxic material originates. This view suggests, furthermore, the possibility of find-

ing some agent which may be antitoxic in action. These examples bring out the point which I wish to emphasize, that theoretical considerations are likely to have highly practical consequences and therefore should be examined with care.

CLASSIFICATION OF THEORIES

Many suggestions have been presented in the past to account for the low blood pressure of shock and for its general phenomena. Some of the views are so obviously untenable in the light of modern knowledge of bodily function that they will not be reviewed here. Any reader who cares to become acquainted with the older ideas will find them expounded in detail in Groeningen's treatise (1), published in 1885. Even after elimination of these older ideas, there remain to be discussed a surprising number and variety of theories which still receive attention.

Any theory which is put forward to account for the development of the persistent low blood pressure of shock must do so in terms of the three factors which already have been described as maintaining the normal circulation. These are the heart, the vasomotor or vasculomotor tone ("vasculomotor" used to include not only arterioles, but also capillaries and veins), and the blood volume. I propose to examine the theories of shock in their relation to these factors. In this examination I shall present the views and the evidence for them as given by their propounders and then shall offer comments and criticisms of both the evidence and the inferences wherever they appear to be open to criticism. In the course of such a discussion there is almost necessarily a residual difference of opinion because of varying weight given by investigators to the evidence which is adduced. Nevertheless it seems desirable to attempt to arrive at a true evaluation of agencies which operate to produce shock even though there may not be at the end a complete agreement or a settled, commonly accepted explanation.

It will not be necessary to review in any detail the theories attributing to the heart a primary rôle in the incidence of shock. Already, in an earlier chapter (see p. 25), the cardiac factor in shock has been considered, and evidence has been cited to show that neither in the nervous control of the heart nor in the action of cardiac muscle is there a defect which would account either for the prompt reduction of pressure in primary shock or for its gradual

reduction in secondary shock. The cardiac factor may therefore be dismissed without further consideration.

Among vasculomotor theories some are concerned with loss of vasomotor tone (that is, with relaxation of arterioles), others with changes in the veins, and still others with a distention of capillaries. These views will be described and considered in that order.

THE THEORY OF INHIBITION

In 1908 Meltzer (2), after discussing various theories of shock, offered one of his own. His theory developed from a series of experiments in which he noted that simple dissection of the skin over the abdomen induced a reflex inhibition of normal peristalsis. These observations were made on rabbits. He and Kast (2, p. 581) noted also that exposure of the intestines in the dog was accompanied by indications of diminished sensitivity and great reduction of reflex response. Since suppression of intestinal movements is due to inhibitory influences, Meltzer assumed that the reduction of sensibility likewise implied inhibition, an inhibition of receptive sensory elements. The development of symptoms of insensibility, general apathy and complete muscular relaxation long before the appearance of any sign of cardiac or vascular breakdown, was taken by Meltzer (2, p. 585) to indicate that these are essential elements of shock and preliminary to the later changes. On the basis of these considerations Meltzer (2, p. 587) ventured the assumption that "the various injuries which are capable of bringing on shock do so by favoring the development of the inhibitory side of all the functions of the body. The predominance of inhibition makes its appearance at first in those functions which are of less immediate importance to life, and are, therefore, less insured by safeguards protecting their equilibrium. With increased injury the inhibition also spreads to the more vital and therefore better protected functions of the nervous system. The early inhibition, in the development of shock, of the functions of lesser importance, might even be looked upon as being, in a degree, conservative measures for the protection of other more important functions of animal life. The restfulness of the body, the painlessness, and mental indifference are certainly most desirable conditions in the management of shock of the more vital functions."

The outstanding phenomena on which Meltzer based his view

are those of cessation of gastric and intestinal movements. Here indeed inhibition is seen; it is, however, not due to *inhibition of activity* in the central nervous system; instead, it is due to *activity* there.

The stimulation of afferent nerves is known to cause discharges along sympathetic pathways which check the contractions of the alimentary tract (3). The inhibition of these contractions may be interpreted, therefore, as the result of special responsiveness of the central nervous system and a resultant delivery of sympathetic impulses.

So far as the apathetic and lethargic condition of the animal in shock is concerned, that also is probably not the consequence of inhibitory central processes. As E. L. Porter (4) has shown, manipulation of the intestines will induce in a spinal reflex a rise of threshold, that is, an obstacle to ready passage of nerve impulses. The lack of responsiveness observed by Meltzer may thus be reasonably accounted for.

The most significant aspect of developing shock and possibly its central feature, namely, the falling arterial pressure, Meltzer did not especially consider. There is no sign of inhibition of the heart or respiration or any other essential function. At the time that Meltzer wrote, moreover, the evidence that the low pressure may be rationally accounted for as due to a reduction of blood volume, had not been established. And although Guthrie (5) has expressed the belief that in "acute psychic shock inhibition probably plays a leading rôle," the suggestion that the severer forms of traumatic shock are due to "predominance of inhibition" may be regarded now as having little support.

THE THEORY OF VASOMOTOR PARALYSIS

This view was first propounded by Mitchell, Morehouse and Keen (6) in 1864. It was elaborated in 1870 by Fischer (7) who in support of it called attention to Goltz's now well-known "Klopversuch." As mentioned earlier (see p. 22) Goltz's experiment, which was performed on the frog, consisted of the infliction of repeated slight blows over the abdomen. The consequences are stoppage of the heart and a lessening of vascular tone, not only in the abdominal cavity but generally throughout the body. A relatively large quantity of blood thereby becomes stagnant in the relaxed vessels, chiefly those of the splanchnic area; the heart when it resumes beating receives only a small quantity of blood and there-

fore the output is meager; the skin is anemic, pale and cold because of the central stagnation.

The theory of reflex vasomotor paralysis can account for some of the phenomena of shock. It is impossible to deny that in acute or primary shock, such an effect as Fischer assumes in consequence of injury may occur. The observations reported in previous chapters, however, have shown that the facts of secondary shock do not support this theory. Thus, for example, the absence of distention of abdominal veins which has been noted when shocked men are operated upon (see p. 39), and the evidence of vasoconstriction in the early stages of shock (see p. 20), are both well defined facts of the shock state which do not harmonize with the idea of a vascular paralysis accompanied by stagnation of blood in abdominal vessels. Furthermore, this theory, like Meltzer's theory of inhibition, was propounded before the reduction of blood volume in shock was known, a fact which gives an adequate explanation of the lowered pressure. Thus, though we admit that reflex paralysis may occur immediately as a consequence of severe injury and thus may perhaps account for certain aspects of primary shock, it does not offer an adequate conception of the phenomena of secondary shock.

THE THEORY OF EXHAUSTION

In their account of "Reflex Paralysis," Mitchell, Morehouse and Keen (6, p. 17) suggested that a serious wound may cause either paralysis of vasomotor nerves or directly destroy the vital powers of a center, and if the vasomotor center, possibly also centers of motion and sensation. This suggestion of an actual injury to the nerve cells was made in 1864; it was amplified by Groeningen (1) in 1885, and was later combined by Warren (8) with Hodge's observations on changes of nerve cells in fatigued animals.

The modern expression of the theory of exhaustion is chiefly associated with the experimental and clinical studies of Crile and his associates (9). They produced shock experimentally by crushing the paws, or burning the skin, or removing part of the integument, or stimulating afferent nerves, and commonly by manipulating the intestines in addition. All the traumatic procedures, which were performed under full surgical anesthesia, were directed towards violent and unusual excitation of afferent nerves. It should be noted, however, that exposure and handling of the intestines would

be accompanied by local inflammatory processes with attendant vascular congestion. Mann (10) testifies that after hours of traumatization of the great nerve trunks he was unable to produce shock in anesthetized animals, and that the only invariably successful method was that of exposing the intestines. More recently Guthrie (11) has reported the production of shock in anesthetized animals by stimulation of the sciatic nerves and the brachial plexus, or this in addition to intestinal injury. Wiggers (12) likewise has produced, by prolonged tetanization of sensory nerves, or by crushing the testes, what he has called "central nervous system shock" —a state of apathy and failure to respond to various kinds of stimuli even after anesthesia was removed. This state may not be accompanied by circulatory failure. The different observers testify that animals vary greatly, that whereas some animals readily succumb to nerve stimulation, others are extremely resistant, and are "shocked" only when the abdominal viscera are manipulated. Wiggers does not express an opinion regarding the nature of shock, except to differentiate between "central nervous system shock" and "circulatory failure"—the lowering of blood pressure. As stated before, Guthrie (13) attributes the depression of function to inhibition. Clinical testimony regarding the relation of nerve stimulation to shock has been given by Vincent, the French neurologist (14), who had experience in forward areas during the War. He states that he never saw a case of shock resulting from either central or peripheral injury of the nervous system.

In his initial examination of shock, Crile (9) assumed that failure of blood pressure was the primary and sole cause of all the symptoms and that this was due to exhaustion of the vasomotor center. His later concept of the pathology of shock has arisen from general biological ideas. He points out that organisms are adapted to react in protective ways to harmful stimulation and that such reactions may be anticipated through worry and fear. Both the reactions and their anticipations in mental states are expressed in the activation of certain organs of which Crile emphasizes especially the brain, the liver and the adrenal medulla. When the response of these organs is excessive, the normal equilibrium is profoundly disturbed; catabolism with extra exhibition of energy exceeds anabolism. When stimuli are intense enough or protracted enough, the result is an extreme demand on the cells and consequent exhaustion and shock. Shock, therefore, may be produced by diverse

causes, such as fear and worry, physical injury and infection, all conditions which, according to Crile, bring prominently into action the organs of defense. Similar opinions have been expressed by Bertein and Nimier (15). This is the kinetic view of shock, that is, that exhaustion is the natural result of overaction. On the basis of these ideas Crile (16) has devised the so-called "shockless operation" in which worry and anxiety and the rough manipulation of tissues are reduced to a minimum.

Morphological Evidence.—The evidence adduced to support the view that shock is a consequence of exhaustion is both morphological and functional. The main testimony has come from a study of nerve cells taken from shocked animals. It is Crile's belief that these cells undergo a series of changes characterized first by hyperchromatism, later by chromatolysis, eccentricity of the nucleus, ruptured membranes and finally by disintegration. Such changes may be induced not only by severe injury, but also by emotion, starvation, insomnia, etc.

The central tenet in Crile's program of a shockless operation is that the operative procedure itself is capable of inducing in nerve cells the pathological changes which he has described. The tenet offers an opportunity for experimental test. This has been made by Forbes and Miller (17) in the Harvard Physiological Laboratory. They applied to the upper stump of the central nervous axis, in a decerebrate animal, electrodes connected with a string galvanometer. The decerebrate preparation, when out of anesthesia, showed a typical hind-limb spinal reflex (for example, the flexion reflex) when the sciatic nerve was stimulated. This was associated with nerve impulses which passed up the cord and which registered electrical changes in the galvanometer. After this relation had been proved to exist the preparation was anesthetized until the spinal reflex disappeared. Thereupon the impulses passing up to the brain-stem likewise disappeared or were greatly reduced; in other words, the degree of anesthesia which blocks the passage of impulses in the reflex arcs of the cord, and which renders an animal inactive, is sufficient to protect the brain against afferent impulses coming in from the surface. These results might reasonably have been anticipated, for there is no evidence that a general anesthetic selects motor nerves or their junctions as regions to be peculiarly influenced and leaves unaffected afferent nerves or their junctions; indeed, the very word "anesthesia" implies an effect on the sensory side.

The absence of any real occasion for cellular changes from trauma under conditions which Crile has stressed, suggests a defect in the rationale of his views.

As previously pointed out (see p. 98) Dolley, who coöperated with Crile in the earlier histological studies, has admitted that hemorrhage produces in nerve cells the same alterations that are seen in shock. The suggestion is reasonable that any cell alterations that may occur in shock, and that may be seen when the nervous tissue of shocked animals is examined, are consequences of the low blood pressure which has prevailed rather than its cause. We have already noted (see p. 99) that Mott has thus interpreted the nerve-cell alterations in shock cases which he has studied. Crile himself has given testimony in favor of this suggestion, for he has reported that if the blood pressure is maintained by transfusion into a shocked animal, a much more severe traumatization is required to alter the cells than is needed when shock takes its natural course. Possibly in further investigation toxic substances set free in the body during shock (see p. 144) will be found to coöperate with low blood pressure in accounting for the changes not only in the cells of the brain but also in those of the liver and adrenals that Crile has described.

Though the testimony from competent observers—Dolley (18), and Kurtz (19)—is concordant that there are typical histological changes in nerve cells after shock and hemorrhage, it should not be forgotten that such evidence is subject to grave mischances in technic and interpretation. Both Allen (20) and Kocher (21) have examined nervous tissue from shocked animals and have declared that the cytological changes which are seen lie within the limits of normal variations.

Differences in the appearance of the cell bodies of neurons from diverse parts of the brain might perhaps be regarded as indicating a definitely directed agent such as nerve impulses, rather than a general agent such as low blood pressure, at work inducing the changes. The differences are explicable, however, on the ground that neurons are differentially sensitive to anemia (see p. 97). Thus by exposure to inadequate circulation they would be differentially affected.

Functional Evidence.—The functional evidence for exhaustion of nerve cells in shock, at least in the early stages, is wholly lacking in Crile's experiments. Already I have summarized (see p. 19) the experimental testimony that the vasomotor center is especially capable of withstanding adverse influences and that only endangering circumstances are required, such as lessened blood supply, in

order to make it become more than usually active. Thus, in the early stages of secondary shock, when the blood pressure is falling, the peripheral vessels are constricted rather than relaxed; we may infer, therefore, that there is then no true exhaustion of the vasomotor center. And the response of the center to afferent stimulation even in the late stages of shock (see p. 18) proves that the inference is correct.

The evidence from functional disturbances that parts of the nervous system other than the centers which control the circulation are *exhausted,* in any strict sense of that term, is meager. In clinical cases, even when the blood pressure has been much reduced, the intelligence usually remains clear. The patient may be restless rather than somnolent and often exhibits surprising muscular power. Cowell (22) reported no reduction of the strength of grip in shock and he observed one wounded man, pulseless and showing a systolic pressure of approximately 30 mm. Hg., who was so vigorous in his movements that two orderlies were required to hold him on the stretcher. Earlier writers on shock have called attention to "prostration with excitement," and the "delirium traumaticum." In these states, however, sufficiently accurate observations were not made to yield us certain proof that shock was actually present.

In many of the states of depression and shock produced experimentally, the intestines were handled vigorously and extensively. As I have indicated before it is unnecessary to assume inhibition as the result of such a procedure. It is equally unnecessary to assume fatigue and exhaustion. E. L. Porter's observations (4) show that there is prompt rise of reflex thresholds when the intestines are manipulated and that the threshold falls more or less slowly after manipulation ceases. A rise of threshold is equivalent to partial blocking of nerve impulses, probably at synapses, but it is not so fundamental a change as exhaustion. It can well account for the signs of depression seen after prolonged nerve stimulation and the handling of abdominal viscera.

Because of the equivocal and uncertain character of the morphological evidence and the lack of cogency of the functional evidence I feel unable to follow Crile in his suggestion of a *primary* exhaustion in shock. As previously stated, however, continued low blood pressure may cause in sensitive nerve cells such *secondary* damage that all that Crile has claimed may be present. In that case the histological changes

he has emphasized would be accounted for as the consequence but not as the cause of the pathological state.

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CHAPTER XVI

DISCUSSION OF THEORIES OF SHOCK (*Continued*)

THEORY OF FAT EMBOLISM

In 1885 Groeningen (1) called attention to observations of numerous medical investigators who had reported that fat from long bones and from subcutaneous connective tissue could be taken up in the blood stream after injury of these regions, and by embolism could lead to a rapid death accompanied by severe dyspnea or acute edema of the lungs. He quotes Nussbaum as follows:

The patient, who perhaps some hours after an accident has had an amputation and has been in good condition for 20 hours or more thereafter, suddenly feels great anxiety and suffers air hunger. The temperature rapidly falls to 34°—35°, and the pulse becomes impalpable and rapid. The mode of death is of course not new. In every century many men have thus died, but only in recent times has this mode of death been put in the category of shock, in which, however, it does not belong.

Groeningen remarks that when, after an interval of well-being, a patient suffers from pallor, irregular action of the heart, dyspnea, hemoptysis, cramps, paralysis, and has fat in the urine, only a very unskillful person would mistake the state for shock.

In 1913 Warthin (2) published a monograph in which he likewise described the varying symptomatology and pathology of fat embolism, with predominating low arterial pressure, venous congestion, symptoms of collapse, Cheyne-Stokes syndrome, etc. The object of Warthin's discussion was to show that surgeons have frequently mistaken fat embolism for shock, or something else, instead of making a correct diagnosis; and in a later publication (3, p. 403) Warthin repeats with emphasis that fat embolism is a distinct clinical and pathological entity, not to be mistaken for shock.

There is no doubt that in the fracture and smashing of long bones, and in the tearing of fatty tissues, fat is liberated in such

manner that it enters the circulation and often can be found accumulated in considerable amount as emboli in the lungs and also scattered in peripheral capillaries. The early authorities cited by Groeningen made such observations and they have been confirmed more recently by Warthin (2), by Bissell (4) and by Siegmund (5).

Experimental Evidence.—Although Groeningen, Warthin and others have called attention to clinical differences between shock and fat embolism, Bissell and W. T. Porter have each suggested that shock may be accounted for by the plugging of vessels with fat. In experimental support of this theory W. T. Porter (6) reported results noted in eight cats into whose jugular veins he injected from 2 to 4 c.c. of olive oil or thick cream. The blood pressure fell to one-half or less of the normal level and, according to Porter, the clinical picture was similar to that of traumatic shock in human beings. No records or detailed protocols have been published. At about the time of Porter's first paper, Bissel (4, p. 17) described the effect of the injection, in repeated doses of varying amounts, of olive oil into the veins of a dog. The first doses were without effect. Finally, however, an injection caused the venous pressure to rise abruptly and the arterial pressure to fall gradually, and the animal soon died. These observations were extended by Simonds (7), who by simultaneous registration of arterial and venous pressures proved that the introduction of fat into the venous stream causes a gradual fall of arterial pressure coincident with a rise of venous pressure. Large amounts of olive oil were needed to produce these results—approximately 1 c.c. of oil for each 500 grams of body weight—before a lasting fall in arterial pressure was produced. Wiggers (8) also has examined the effects which result from introducing oil into veins and has confirmed the observation that the gathering of fat in the pulmonary vessels will cause a marked fall of arterial pressure.

In a later paper, W. T. Porter (9) has argued against the hypothesis that shock follows from fat emboli in the lungs, because he has been able to induce a lowering of blood pressure by injecting minute quantities of fat into the vertebral artery, which supplies the vasomotor region. No records or details have been given. In order to avoid pulmonary emboli, Wiggers (10) likewise has introduced oils and emulsions into the arterial circulation. Such injections had variable effects. In some cases large quantities could

be injected without apparent effect on arterial pressure; in other cases a temporary rise was followed by gradual return to normal, and in others the pressure, after a slight rise, rapidly fell, and within a few moments the animal was dead. In these last cases, death was attributed to respiratory failure brought about by fat emboli in the medulla. In none of the cases did the circulation fail as it does in shock. Wiggers concluded, therefore, that neither the intravenous nor the intra-arterial injection of fat produces changes in the dynamics of the entire circulation which are comparable to those found, for example, after exposure of the intestines.

Clinical Evidence.—Two sorts of propositions have been made as to the part played by fat embolism in the production of clinical shock. Bissell (4, p. 22) and Sutton (11), for example, suggest that clogging of pulmonary capillaries is the occasion for the shock phenomena, and Porter (12) thinks that these phenomena are due to disturbance of the blood flow in the medulla. A noteworthy aspect of these explanations is the lack of evidence to support them. If the plugging of pulmonary capillaries is the cause of trouble, the patient should show signs of air hunger or dyspnea. There should be pulmonary edema and even hemoptysis. On auscultation, râles should be heard. Furthermore, the veins should stand out prominently because of gradually increased venous pressure. In dozens of cases of shock which I have observed, the symptoms mentioned above have not been present. As already stated (see p. 14), the veins instead of being prominent from increased pressure are actually small and difficult to enter. Moreover, as Crile (37) has noted, the theory of fat embolism fails to account for (*a*) the shock seen when abdominal injuries are accompanied by penetration of hollow viscera and not seen when penetration does not occur, though the same fat areas have been traversed; (*b*) the shock from burns; and (*c*) the shock from head and chest injuries.

On the other hand, if shock is to be attributed to plugging of bulbar capillaries, it is surprising that any one should think that the vasomotor center would be uniformly and exclusively picked out in a group of vitally important centers very closely related to one another in the floor of the fourth ventricle. If on this theory, the vasomotor center were as frequently affected by fat emboli as might be expected from the number of cases of shock seen after the smashing of tissues and the breaking of bones, the swallowing center and the respiratory center should be frequently disturbed at the same time. Such, however, is

not the case. Furthermore, in demonstrated cases of fat embolism there are effects on the other parts of the brain than the medulla—stupor, cramps, and paralyses. The temperature usually rises, even as high as 104° — 105° F. These symptoms are not at all characteristic of clinical shock.

Because of the striking differences, both experimental and clinical, between the phenomena of shock and those of fat embolism, therefore, and also because of the lack of evidence in clinical cases that fat globules, either in the lungs or in peripheral capillaries, have produced the low blood pressure which is observed, we are justified in concluding that shock is not due to the liberation of fat into the blood stream in any considerable number of cases, if at all.

Breathing CO_2 as a Treatment for Fat Embolism.—In shock, according to Porter (13), the blood is pooled in the large abdominal veins. He would have it restored to the circulation by using the diaphragm more vigorously than normally to pump the blood from the abdomen into the thorax. Consequently, he proposes to have persons who are shocked breathe an excess of carbon dioxid in order to stimulate maximally the respiratory center.

There is no evidence that in shock, blood is accumulated in the abdominal vessels (see p. 39). Even if the blood were there, however, the procedure suggested by Porter is of questionable value. As Wiggers (8, p. 511) has remarked, in cases where arterial pressure is low because of pulmonary fat embolism, the right heart is already in difficulty because of accumulated obstacles between it and the left heart. To force more blood on the right heart for it to push through the narrowed channels of the lungs might be the worst possible procedure, for it might embarrass the right ventricle to such a degree that continued contraction would become impossible. On the other hand, if the very improbable assumption is made that there is no fat in the lungs, or very little fat, but that the vessels of the medulla are plugged, no permanent advantage can be obtained by extra activity of the diaphragm. According to Warthin (3, p. 401), when fat embolism has reached such a degree as to become clinically manifest in symptoms resembling those of shock and collapse, minute cerebral lesions, hemorrhages and infarctions have already occurred which "cannot be remedied by respiratory pumps."

Porter has reported figures in only one case (14) which permit judgment to be made as to the effect of his method: the diastolic

pressure at 11:05 was 53 mm. Hg.; at 11:15 the patient began to breathe an excess of CO_2 and the pressure rose to 60 mm.; at 11:25 he stopped breathing CO_2-rich air and the pressure fell to 53 mm., that is, back to the original level. In other words, the effect was only temporary and in the absence of accumulation of blood in the abdominal veins may be accounted for by the well-known effect of increased H-ion concentration (due to excess of CO_2 in the blood) in stimulating the vasomotor center (15).

THEORY OF AN ADRENAL FACTOR

Two suggestions have been offered as to the relation of the adrenal glands to the state of shock: one that shock may be due to overactivity of these glands; the other that it may follow their exhaustion.

Adrenal Hyperactivity.—The first intimation that overactivity of the adrenals might occasion shock was made by Bainbridge and Trevan (16) who based their experiments on the evidence of adrenal secretion during extreme emotion or severe pain. They slowly injected adrenalin into a systemic vein for 20 minutes or longer, at a rate sufficient to maintain arterial pressure at a supernormal level comparable with that attained during moderate stimulation of a sensory nerve. When the injection of adrenalin was stopped, the arterial pressure rapidly fell, while the portal pressure remained high; the animal passed into a condition of shock, with feeble pulse and shallow respiration. Hemoglobin and hematocrit determinations revealed a steady decrease in blood plasma in relation to the corpuscle content. These observations were confirmed by Erlanger and Gasser (17), who attributed the failure of the circulation to the extreme slowing of the blood flow throughout the body caused by the vasoconstrictor action of the injected adrenalin. These positive results Henderson, Prince and Haggard (18) failed to obtain, though they held the blood pressure at a high level for periods varying from one-half to two hours by constant and also by intermittent adrenalin injections. Most of their animals died of acute cardiac dilatation.

The positive results above recorded were obtained by amounts of adrenalin (6 to 11 c.c. of a 1:1000 solution in Erlanger and Gasser's experiments) far beyond any which have been evoked by reflex stimulation. The shock which follows these huge injections

must be regarded, therefore, as wholly unlike any probable consequence of adrenin set free by the glands in the body. Furthermore, there is a difference of testimony regarding the secretion of these glands in shock. Although Bedford and Jackson (19), and later Bedford (20), reported finding the adrenin content of the blood increased when the blood pressure is low, Stewart and Rogoff (21), using the same method which Bedford used, obtained negative results. This method, which involved opening the abdominal cavity and manipulating the intestines, might in itself induce a state of shock. Indeed, the progressively slower flow of blood through the adrenal veins in the course of Stewart and Rogoff's experiments (22), as reported in earlier papers not concerned with shock, indicates a gradually falling arterial pressure. In recent studies by Rapport at the Harvard Physiological Laboratory, the denervated heart was used as an indicator of adrenal secretion, and shock was induced by tissue injury in one of the hind legs. In some instances, an increased heart rate gave clear evidence of a greater adrenal discharge, but occasionally the increase failed to occur. No proof exists, therefore, that the adrenal glands secrete in such excess as to favor the development of shock. Even were they overactive, they would only be supporting the vasoconstrictor impulses brought into play as the blood pressure tends to drop—a mechanism which may have been operating in certain of Stewart and Rogoff's cases.

Adrenal Exhaustion.—The other suggestion which has been offered is that shock follows from exhaustion of the adrenal glands. Sweet (23) testifies that only by removal of the glands from lower animals has he been able to produce symptoms resembling shock in human cases, and Corbett (24) has published figures, without, however, giving details of his methods, which suggest exhaustion of the glands in cases of trauma, ether anesthesia and infection. On the other hand, Short (25), who used a very delicate test, reported that the adrenin content of the glands in fatal cases of shock is not noticeably reduced.

Whatever the evidence may be regarding exhaustion of the adrenal medulla, there is no proof that adrenin is at all essential for the maintenance of a normal blood pressure. As Hoskins and McClure (26) have proved, a degree of adrenin which affects blood pressure checks the movements of the stomach and intestines, an effect which would obviously upset the organism fundamentally if adrenin were needed to support blood pressure. Further, Aust-

mann, Halliday and Vincent (27), and more recently Gley and Quinquaud (28) have shown that after removal of the adrenal glands, the blood pressure does not tend to fall for many hours, and that none of the vascular reflexes are affected. The theory that adrenal secretion is needed to keep blood vessels in tone has had to be given up. Exhaustion of the adrenal medulla, therefore, even if it were proved to be present, would not account for shock. The testimony of Mann (29), that total excision of the adrenals does not reproduce the phenomena of shock, is in harmony with this inference.

Neither the suggestion of overactivity nor the suggestion of underactivity of the adrenals has sufficient evidence in its favor to warrant attributing shock to the adrenal glands.

THEORY OF "ACIDOSIS" AS A SHOCK FACTOR

The correspondence between the degree of reduction of the blood alkali and the degree of reduction of blood pressure, to which attention has been called (see p. 53), early hinted that there might be, not only a lower alkali reserve produced by the low pressure, but also a lowering of the pressure because of the reduced reserve and possible increase of the H-ion concentration in the blood. The previous observations of Hooker (30), Gaskell (31) and Bayliss (32) that small amounts of acid substances would cause relaxation of vascular muscle, and Patterson's (33) discovery that when H-ions are increased by CO_2 in the blood, cardiac muscle relaxes to a greater extent and contracts less forcibly, so that the output is diminished, and also Ferrai's (34) testimony of increased viscosity of the blood with increase of CO_2 content seemed favorable to a continuance or augmentation of a low blood pressure as acidosis develops. It was suggested, therefore, that however the initial fall of pressure might be produced, the consequent reduction of the alkali reserve (development of "acidosis") might locally relax vessels which are not under nervous control, might weaken cardiac contraction, and might increase the viscosity of blood, so that the dangerous condition which had been established would be made worse. The striking improvement in the condition of patients suffering from shock, and showing by their respiration that extreme "acidosis" was present, that was wrought when sodium bicarbonate was injected, indicated that the state was one which could be improved by increasing the alkali reserve (35).

When the foregoing ideas were subjected to critical examination and to further experimental tests, it was found that the increase of carbonic acid or H-ions in the blood, required to bring about the changes which observers had reported, would have to be much greater than would naturally be produced by any bodily changes, either physiological or pathological.[1] Furthermore, Dale and Richards proved that the CO_2 capacity of the blood could be reduced to a very low figure (for example, in different instances, from 44 volumes per cent to 8.6; from 36.1 per cent to 8.8; or from 37.1 per cent to 18) with no permanent change in the blood pressure (36). To be sure, these experiments were performed under ether anesthesia, and as the alkali reserve was reduced by acid injection, the sensitiveness to ether became marked and the amount given had to be considerably reduced.

After hemorrhage and consequent low arterial pressure, or after a fall of blood pressure due to decerebration or pithing (36, p. 261), the alkali reserve is reduced (that is, an "acidosis" is developed) just as it is after prolonged low blood pressure caused by increasing the intrapericardial tension (see p. 65). The common result of these various procedures emphasizes the cardinal importance of maintaining an adequate oxygen delivery to the tissues. In the treatment of a low alkali content of the blood, therefore, the important matter is not to increase the sodium bicarbonate of the blood in the late stages of shock, but to restore early the essential lack—the needed oxygen—by a better blood supply, or, preferably, to prevent reduction of the alkali reserve by providing adequate oxygen through early improvement of the circulation.

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[1] The results of this analysis, issued under the title, "Acidosis in Relation to Shock and Hemorrhage," by the English Medical Research Committee (March, 1919), seem to have been overlooked. For example, Raymund has since published an extensive article (Am. Journ. Physiol., 1920, 53; 109) on the alkali reserve in experimental shock, in which he has criticized some informal notes sent by me as a member of the English Shock Committee, as suggestions to members of the American Committee, but naturally not intended for publication, and has entirely missed the full discussion of the question made public more than a year previously by the group in England.

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CHAPTER XVII

DISCUSSION OF THEORIES OF SHOCK (*Continued*)

THEORY OF ACAPNIA

The acapnial theory of shock, which was first formulated by Henderson (1) in 1908, has been developed by him in an extensive series of papers. Henderson's views have received much attention in the literature of shock and have been the subject of a good deal of controversy. In order to understand his position well we must recognize that during the course of his investigations his views have changed with the appearance of new evidence.

In one of the early investigations of Henderson's series (2) he made to our understanding of shock an important contribution by pointing out that the failure of the circulation is due to an inadequate return of venous blood to the heart. He noted (3) that in their first effects shock-producing procedures might reduce the blood flow through the heart more than 60 per cent, although normal arterial pressure was maintained. The acapnial theory is directed toward an explanation of the diminished venous return.

Pain, sorrow, fear and etherization, according to Henderson, will each induce excessive respiration. Thereby the carbon dioxid content of the blood will be reduced, that is, a state of *acapnia* will exist. The sequence of events in acapnial shock he lists as follows (2, p. 175): (*a*) hyperpnea; (*b*) acapnia; (*c*) failure of the venopressor mechanism; (*d*) venous anoxemia, tissue asphyxia and acidosis; and (*e*) acute oligemia. There is no question that excessive respiration will reduce the CO_2 content of the blood, as Henderson's data prove. A discussion begins, however, as soon as this fact is interpreted in relation to shock. In considering Henderson's observations and explanations, we shall gain clearness by treating them separately in their different aspects.

Pain and Hyperpnea in Shock Cases.—With reference to Henderson's primary assumption that severe wounds are associated with such pain that very vigorous respiration and consequent acapnia ensue, it may be stated that observed facts fail to support it. The severely wounded almost universally testify that they do

not immediately experience pain. "On nothing is there greater unanimity," Groeningen (4) wrote, "than on the extraordinary and remarkable fact that the wounded suffer no pain or only slight pain at the moment of being struck." In support of this statement, he quoted numerous military surgeons and others who had had occasion to study shocked men. When questioned regarding their feelings, the wounded usually testify to having felt a dull blow, but not severe pain. A man who had one hand blown off informed me that he knew something had struck his hand and then thought that some object was hanging at his wrist. Only when he attempted to shake the object off did he realize that it was his own hand, attached by a shred of skin. Crushing and tearing agents seem to deaden the nerves for some distance back of the exposed surface. As Groeningen (4) has remarked, pain begins to appear first in such instances only with the development of inflammation.

In the severely wounded, also, there is absence of such vigorous hyperpnea as Henderson's theory requires. Cowell paid particular attention to the respiration in shock cases in front areas and on their way back, and never observed hyperpnea. In the casualty clearing station, the typical form of breathing already noted (see p. 55), though faster than normal, is superficial. As Edsall (5) has pointed out, breathing of that character brings about a less effective ventilation of the lungs than normal breathing, because the to-and-fro tide of air occurs to a larger degree in the "dead space," that is, in the upper reaches of the respiratory channel. In these conditions the alveolar CO_2 and consequently the concentration of carbonic acid in the blood would certainly not be reduced. Furthermore, even when the most extreme hyperpnea is carried on voluntarily, no shocklike condition results (5, p. 645). And in cases of almost intolerably severe pain, such as is experienced in facial neuralgia, there are no shocklike phenomena produced, either by the ways Henderson has suggested or in any other way. Furthermore, in experimental shock, as noted by Aub (see p. 60), there is no definite and uniform correlation between excessive breathing and a low blood pressure.

The foregoing observations negative Henderson's view that shock is associated with intense pain and with such respiratory activity as to pump out the CO_2 from the blood.

Acapnia in Relation to Shock.—At first Henderson declared that acapnia, if prolonged, would bring about an abolition of tone in the

veins and that the circulation would fail because of venous stagnation (2, pp. 362, 363). This view was built into the concept of a peripheral venopressor mechanism which is subject chiefly to chemical control—deficiency or excess of CO_2. The experiments reported by Hooker (6), by Schwartz and Lemberger (7), and by Anrep (8), however, agree in proving that increase of carbonic acid in the blood produces peripherally a *relaxing* effect on blood vessels. This peripheral influence, as Hooker (9) demonstrated, may be overwhelmed by an asphyxial stimulation of the nerve centers which constrict the veins. The consequence will be a rise of venous pressure. More recently Henderson (10) declares that he has been misunderstood, that his view was that acapnia would cause constriction of the veins, that is, increased venous tone, and thus would lower venous pressure by damming back the blood in the capillaries.

Henderson now states (10) that a high content of CO_2 in the blood raises venous pressure by a relaxation of the venules, and that this permits "a readier outflow from the 'tissue reservoirs' "—an expression which is not defined. We have previously seen (see p. 33) that there is no evidence of a sufficient accumulation in the capillaries to warrant their being regarded as "tissue reservoirs." If blood in the usual proportion of plasma and corpuscles is not gathered in large volume in capillary areas, obviously relaxation of venules cannot release it.

Hill and Flack (11) and later Janeway and Ewing (12) attributed the form of experimental shock which Henderson produced by vigorous artificial respiration, not to acapnia but to prolonged mechanical interference with the circulation, which would result from overdistention of the lungs and extra pressure on the pulmonary capillaries. Furthermore, Janeway and Ewing (12, p. 173) proved that quite as severe shock could be produced by artificial hyper-respiration and by intestinal manipulation when the CO_2 content of the blood was maintained at a high level as when it was allowed to fall to a low level.

The foregoing data show that the rise of venous pressure on breathing an excess of CO_2 is reasonably accounted for by the well recognized increase of vascular tone from stimulation of vasculomotor centers, and not to a peripheral venopressor mechanism; that the hypothesis of "tissue reservoirs" where blood may be stored is unwarranted; and that the experimental procedure used by Henderson to produce both acapnia and shock may be used to produce shock without acapnia. The support for the acapnial theory is thus proved to be highly questionable.

Acute Oligemia in Shock.—Besides the idea that blood is stagnant in peripheral vessels Henderson (2, p. 163), following Sherrington and Copeman and also Malcolm (see p. 43), early expressed the important idea that there might be an actual diminution of volume of the circulating blood. His concept of the mechanism by which this would be brought about was that, through failure of oxidative processes, the tissues would become asphyxiated, the hydrophilic property of the colloids would consequently increase, and water therefore would pass from the blood to the asphyxiated cells and to the tissue spaces. This idea has had confirmation in a modified form in the recent studies which have proved a reduction of blood volume in shock, a reduction, however, that involves the plasma as a whole and not merely the escape of water (see p. 44). Henderson seems not to have laid stress on this idea in his own work and has brought no data himself to support it.

"The Usual Form of Death in Shock."—In 1908 and 1910 Henderson supported the acapnia theory by experiments in which vigorous artificial respiration was carried on, or hyperpnea was induced, by intense afferent stimulation. In the former cases, the heart contracted at a high rate and with only partial relaxation ("cardiac tetanus"); there was an attendant fall of blood pressure (1, p. 142). The published records of the latter experiments (13) reveal no drop in blood pressure either during the hyperpnea or in the early stage of the apnea which naturally follows. The primary failure of the circulation is of *cardiac* origin and is attributed by Henderson (2, p. 157) to oxygen starvation of the heart.

In death from actual shock under clinical conditions, however, there is never, in my experience, a sudden exit of this character due to violent pulmonary ventilation. The blood pressure gradually falls and the breathing has the characteristic shallowness previously described, except in cases of terminal acidosis, when the deep respiratory movements are due to blood changes, not to pain. In experimental conditions, likewise, such results as Henderson has noted have not been observed by others. Wiggers (14) has recently stated that even when very deep breathing had continued for the greater part of two hours as a consequence of afferent stimulation, in no instance of his series did permanent apnea or death ensue from respiratory failure. Furthermore, in a form of experimental shock which closely resembles shock in man, the blood pressure gradually falls to a shock level although the respiration is kept moderate and uniform by artificial means (see p. 147).

Diminished Blood Alkali and Shock.—In recent papers Henderson has brought forward data showing that excessive respiration reduces not only the carbonic acid but also the sodium bicarbonate of the blood, and that breathing CO_2-rich air increases both (15). Thus the alkali reserve of the blood may be influenced by the activity of the respiratory center. The lowered alkali reserve seen clinically in shock (see p. 56) Henderson now interprets as due to excessive breathing. In experiments which involved rapidly repeated pushes against the stomach during long periods, with consequent over-ventilation of the lungs, Henderson and Haggard (16) found that an excess of CO_2 in the air breathed by the animal prevented a fall of the CO_2 capacity of the blood, and might, indeed, increase it. On the other hand, if the extra CO_2 was not given, the procedure reduced the CO_2 capacity of the blood as well as the arterial pressure.

Examination of the protocols of Henderson and Haggard's experiments (16) shows that whether CO_2 was administered or not, a reduction of the original CO_2 capacity by more than three volumes per cent was invariably associated with an arterial pressure below 90 mm. Hg. —in all but one case below 80 mm.—and that further reductions of the capacity (alkali reserve) were associated with still lower pressures. As was to be expected, though the CO_2 capacity might be raised by breathing excess of CO_2, and though blood pressure likewise might be thus maintained at a higher level than otherwise, the effects were not permanent, and with the subsequent fall of blood pressure the alkali reserve began to diminish. This latter relation has already been discussed (see p. 60), and, by experiments in which respiration was kept mechanically regular, proof has been given that the reduced CO_2 capacity is not due to excessive breathing. On the other hand, the correspondence between the fall of the alkali reserve and the fall of arterial pressure below a critical level in Henderson and Haggard's experiments (16) confirms the conclusions previously stated (see p. 70) that the effect follows from acid production in the absence of adequate oxygen supply to the tissues.

Underlying the views expressed by Henderson and Haggard, there appears to be an assumption that normal blood pressure depends on the preservation of a rather high CO_2 content and capacity of the blood. When the capacity was pushed below 33–36 volumes per cent in their experiments, they state, the result was fatal (16, p. 371). That some other factor than the mere reduction of the blood bicarbonate was operative is proved by the fact that the CO_2 capacity can be lowered by

injections of acid to less than 9 volumes per cent without any reduction of blood pressure (17).

The Treatment of Shock by Rebreathing.—Henderson, Prince and Haggard (18) have proposed that persons suffering from shock shall be treated by causing them to breathe to and fro through a long tube so that the CO_2 content of the alveolar air, and thus of the blood, shall be increased. This proposal is based on the general theory of acapnia as the cause of shock. As the foregoing discussion has revealed, none of the relations between acapnia and shock, which are postulated by this theory, are fixed—pain and the excessive breathing required for acapnia are commonly absent, shock may exist without acapnia and acapnia may exist without shock, and the low CO_2 content of the blood in shock can be accounted for as the result of the low blood pressure, not as its cause. Under the circumstances, the plan to treat shock by rebreathing of the expired air—in order to restore lost CO_2 and to operate a venopressor mechanism—is irrational. The method takes no account of the loss of blood volume, which Henderson strongly emphasized in one of his early papers (2) as a prime factor in shock, and which is now known to be a central fact in the complex. Furthermore, there is danger lest in the rebreathed air the oxygen content will be so reduced that the condition of oxygen-want, from which the patient may be suffering, will be gravely aggravated. Bayliss and I (19) found that in shocked animals a rise of blood pressure and an increase of the alkali reserve could, indeed, be induced by causing the animals to rebreathe or to breathe an excess of CO_2. The effects, however, were at best only temporary, as in the experiments of Henderson and Haggard, cited above, and quickly disappeared when ventilation of the lungs with good air was again permitted. Similar results in a human case have already been mentioned (see p. 125). In some of our experiments rebreathing was followed by a disastrous fall of blood pressure. The procedure never rendered any permanent benefit.

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CHAPTER XVIII

DISCUSSION OF THEORIES OF SHOCK (*Continued*)

THEORIES OF VASOCONSTRICTION AND CAPILLARY CONGESTION

At various times in the development of the conception of shock the view has been expressed that a prime factor in bringing on the condition is a strong contraction of the arteries. It is reported that Mapother (1), at a meeting of the Surgical Society of Ireland in 1879, brought forward this idea in a statement that the most marked physical change observed in shock is a constriction of the arterioles, with paralysis of the vasodilator nerves. The more recent expositions of this idea have been given by Malcolm (2), by Starling (3) and by Erlanger and Gesell (4).

Malcolm's Theory.—As early as 1893, Malcolm (2, p. 275) put forward the view that in shock the arteries are tensely and actively contracted. The basis for this statement appears to have been the clinical observation that the more profound the degree of shock, the paler are the tissues—pallor of the peritoneum, for example, is noted even when very little blood has been lost (2, p. 275). Contraction of the arteries, according to Malcolm, would tend to cause the blood to collect in the large veins (2, p. 283). As a result there would be increased tension of the "serum" (plasma), which would be expressed from the vessels into the tissues. Thus the total amount of blood would be diminished. The inference that there is actually a reduction of blood volume, Malcolm drew from the marked benefits which resulted when the blood volume is increased (2, p. 302). He ascribed the final low pressure to removal of fluids from the vessels and from the body, and to inefficient cardiac dilation. "Repeated or continuous traumatism may in these ways reduce blood pressure until the vasomotor and other nerve centers are starved, and life cannot be maintained" (2, p. 284). This remarkable explanation of the changes occurring in shock, based almost wholly on clinical observation and inference, was elaborated

by Malcolm more than a decade ago, and, with slight errors, outlines the main features of the course of secondary shock as we understand it to-day. The chief defect in the argument lies in a failure to account for a primary vasoconstriction capable of inducing the effects which Malcolm describes.

Starling's Theory.—This theory (3, p. 371) starts with the now well-known fact that the low blood pressure of shock is due to the small amount of blood pumped out by the heart. The blood has somehow gone out of circulation so that the condition is analogous to that provoked by abundant hemorrhage. Where is the lost blood to be found? It is not in the abdominal veins (3, p. 372), nor in the large veins of the limbs for often they are contracted to such a degree as to render difficult the introduction of a needle or cannula. The essential fact of shock, therefore (3, p. 373), when there is no complicating hemorrhage, is the passage of blood from the general circulation into dilated capillaries; and since the skin is usually pale in shock, the blood is, by exclusion, to be found in the capillaries of the muscles. With the blood stagnant in the capillaries there would be extravasation of plasma through their walls and a consequent concentration of the corpuscles.

How would blood become stagnant in dilated capillaries? Starling (3, p. 373) suggests that under battle conditions men are in a state of great excitement or tension. This state involves not only higher tonicity of the general musculature but also an augmented tonicity of arteries and arterioles. The blood pressure, therefore, is raised. When a man is wounded this hypertonicity is increased, so Starling argues, because of the sudden stimulation of sensory nerves. At the same time, however (3, p. 374), there is an inhibition of all the striated muscles. A sharp shift of internal conditions instantly occurs, that is, an increased vascular tone with a diminished muscular tone. One of the great factors affecting the circulation in the muscles is thus abolished. The blood which continues to flow through the muscles thus tends to remain in them and dilate the capillaries. The vascular system thus gradually becomes too capacious for the blood which it still contains; the blood pressure falls; oxygen is carried to the tissues in less amount; and local acidosis results which provokes further dilation of the capillaries. Moreover, there may be active dilation of the capillaries from direct stimulation of sensory nerves. The final result is a deficient return of blood to the heart and a deficient general circulation. The tissues

(3, p. 375), deprived of proper nourishment, form fixed acids instead of carbonic acid. There is a consequent diminution of the alkali reserve of the blood and an increase of the H-ion concentration. A vicious circle becomes established, for acid diminishes the activity of the heart and also has a tendency to augment the capillary dilation, which may be considered as the prime and essential factor of shock.

Although much of what Starling has suggested may be taken as well supported by evidence, the difficulty remains of accounting for any such sharp alteration as he has inferred, in consequence of the relatively slight rise of arterial pressure. Cowell (5) noted that in times of activity in front-line trenches the systolic pressure varied from 140 to 160 mm. Hg. It is doubtful whether the pressures go much higher than this in actual battle conditions. Such pressures are, of course, well within the range of physiological variation and are constantly occurring and quickly disappearing in the course of everyday existence, without signs of inducing a shocklike state. Also shock may occur when a man is wounded during sleep (5, p. 107) and therefore lacking the hypertonicity required by this theory. Furthermore, Starling's view that the lost blood is in the dilated capillaries of relaxed muscles is not supported by any evidence. And finally, as already pointed out (see p. 128), the acidosis developed in shock is probably not adequate to affect to a marked degree the size of the capillaries. For all these reasons it is improbable that Starling's theory is adequate to account for the facts.

Erlanger and Gesell's Theory.—Erlanger and Gesell and their collaborators (4) produced shock experimentally by exposure and manipulation of the abdominal viscera (4, p. 97), by partial occlusion of the inferior vena cava (4, p. 151), by partial occlusion of the thoracic aorta (4, p. 166), and by intravenous injections of large doses of adrenalin (4, p. 346). All these procedures have the effect of reducing the circulation. The effects of a reduced circulation they related (4, p. 171) to a process observed by Mall and Welch. "When, in an animal, a mesenteric artery is partially or completely occluded, the smaller and the larger microscopic veins become more and more distended with red corpuscles and all of the phenomena of an intense venous hyperemia appear. The red corpuscles accumulate in clumps or in solid columns. This change may become permanent, producing an evident obstacle to forward movement of the blood. The same phenomena of distention with red

corpuscles, clumping and stasis appear gradually in the capillaries. With the partial blocking of the venules and capillaries, red corpuscles begin to pass through the walls of these vessels by diapedesis; and after a time the hemorrhage becomes so great that it is difficult to observe the condition within these vessels." This process begins to occur, according to Mall and Welch, when the pressure in the artery is reduced to about one-fourth or one-fifth of the normal. In all the experimental conditions which they studied, Erlanger and his group of workers (6) found that the most striking change is an extreme distention of the capillaries and venules of the intestinal villi with solid masses of red corpuscles. Along with this change there is a marked reduction of blood volume (6, p. 419). In consequence the volume flow of blood becomes reduced to such a degree that the blood pressure falls in spite of vasoconstriction, and the secondary effects of shock already described, make their appearance.

It is obvious that the general concept of the processes occurring in shock, as described by Erlanger and Gesell, is in accord with views which have been developed in the earlier chapters; in other words, the theories put forward by these investigators take into account and emphasize not only the reduction of blood volume, but the secondary effects which appear in consequence of an inadequate nutrient flow. Erlanger and Gesell, however, like Malcolm and Starling, have failed to produce shock by a procedure similar to that which is effective in human cases. The primary occasion for shock in Erlanger and Gesell's (7) experiments was always a reduced circulation, and they have suggested that pain stimuli and a certain amount of hemorrhage may possibly activate the vasoconstrictor mechanism to such a degree that the circulation will be reduced, much as it is after injection of large doses of adrenin. They did not succeed, however, through stimulation of the vasoconstrictor center, either reflexly or directly, in producing in animals a peripheral constriction of the duration that proved necessary, in their experience with other methods, to start the animal on the road to shock (6, p. 391). The mode of action of the initiating agent in secondary shock is thus left unsatisfactorily explained.

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CHAPTER XIX

DISCUSSION OF THEORIES OF SHOCK (*Concluded*)

THEORY OF TRAUMATIC TOXEMIA

None of the theories thus far discussed has offered a satisfactory account of the initiation of secondary shock. The problem still requires the demonstration of some factor, naturally related to the onset of shock, which may so operate in the body that, when hemorrhage and infection are ruled out, the persistent low blood pressure characteristic of the shock state will become gradually established.

The Wounds Associated with Wound Shock.—A primary consideration in experimental study of natural phenomena is that the reproduction of the phenomena under controllable conditions shall resemble as closely as possible the occurrences in nature. This is a consideration which has been largely neglected, it seems to me, in experimental investigations of shock. No doubt persistent low blood pressure can be produced by a variety of means. As shown by the foregoing review of theories, investigators have reported duplication of certain aspects of shock by protracted stimulation of nerves, by severe and long-continued manipulation of exposed intestines, by vigorous over-ventilation of the lungs, by repeated pushes against the stomach, by interrupting the circulation in large areas of the body, or by injecting into the blood stream relatively large amounts of oil or cream. Although such procedures cause changes similar to those which occur in natural shock they do not reproduce the circumstances which occasion shock after ordinary wounds or injuries. It is obviously desirable to duplicate, so far as possible, the actual conditions which give rise to a shocklike state and then to analyze them in order to determine what factor or factors among them is operative.

The nature of the wounds typically seen in cases of secondary shock may be judged from the following records made at Béthune. In reading these records it should be understood that the wounds

were often made by large, ragged pieces of shell moving at high velocity. When such a missile breaks the humerus or the femur or the ilium, it smashes and tears extensively the overlying muscles which in the thigh and hip form a thick layer. In all these cases shock was present:

E. G. Compound fracture of left ulna and radius, arm nearly severed, wounds of right arm and left side, abdomen opened, intestine and omentum protruding.

C. P. H. Shell wounds of right thigh with fracture of the femur, and of left arm with fracture of the humerus, wounds of the face.

G. D. Wounds of the left arm with fracture, left leg with fracture, flesh wounds of the right thigh and abdomen.

G. J. H. H. Shell wounds of right ankle, of left leg with fracture, and of the muscles of the buttock.

H. J. H. Bursting shell broke right femur, left tibia and fibula, and injured right arm.

A. J. R. Extensive wounds of both legs, left foot and left arm.

W. G. Wounds of buttock with fracture of ilium, also wounds of right foot.

P. K. Fracture of left femur (much comminuted) and right tibia.

W. A. T. Wounds of buttock and perineum, muscles below the buttock torn across and smashed in both legs.

G. K. Wounds of both arms, left thigh, left foot, compound fracture of the right thigh.

R. C. Compound fracture of right femur, multiple shell wounds, left femur, buttock and chest.

A. H. Multiple shell wounds. Large wound of the left loin involving the gluteal muscles, fracture of the pelvis, extensive wound of right calf muscles and the muscles of the left thigh and left calf, and numerous wounds in back and chest.

The general character of war wounds is well described by Wallace and Fraser (1):

The tissues of the wound are crushed and lacerated, and there are widespread contusion and effusion of blood into the surrounding parts. The neighboring blood vessels are often pulped and thrombosed, and as a result of the interference with the blood supply, whole areas of tissue may afterwards die and slough away. In these wounds, muscle appears to be affected more than any other tissue: it becomes a mass of dark brown crushed matter without any evidence of striation or vitality. One cannot fail to be impressed

by the enormous destruction which even a small fragment of shell will produce, a degree of destruction which is apparently quite out of keeping with the size of the fragment: the exaggerated damage depends upon the enormous velocity at which the fragments are traveling.

Experimental Evidence for Traumatic Toxemia.—While I was working with Bayliss in London in January, 1918, we became interested in the question as to whether the acid known to be developed in injured tissue (2) might not be a contributory factor in the production of shock as seen in man (3). The traumatization which we caused induced both an acidosis and a low blood pressure (see Fig. 13). Later it was shown that acid production was not an essential factor in the complex (see p. 128). Some other agent, therefore, must be acting. Further analysis of the mode of operation of the trauma will be deferred until the observed facts are described. These facts were established in part by Bayliss and myself working together (4), and in part by each of us working independently after I was transferred to the Laboratory of Surgical Research at Dijon, France.

In order to bring about in lower animals a traumatization similar to that giving rise to shock in man, the thigh muscles in the anesthetized cat, while being supported by an iron block, were repeatedly struck with a blunt wedge-shaped hammer, or crushed by compression. The trauma usually failed to break the skin, so that infection from without was impossible. Occasionally the femur was broken, but this had no important influence on the results which were seen. After this procedure, the course of events was followed in observations on the pulse, respiration, alkali reserve and corpuscular volume. In Fig. 13 is presented a summary of the changes seen in a typical case. An actual record of the blood-pressure changes of shock produced in this way is shown in Fig. 14.

As Fig. 14 proves, the crushing of the muscles in one hind leg of the cat may have no immediate effect. There may be a momenary rise or fall of arterial pressure. After about twenty minutes, however (and still longer in the dog), the pressure begins to fall; and after about an hour the pressure has usually fallen to 80 mm. Hg. or even lower, that is, to a shock level. There it may persist for several hours. In other words, a general bodily condition resembling shock is produced by duplicating circumstances which induce shock in man. The only noteworthy difference is the presence

of anesthesia (urethane). That this is not a determining factor is shown by use of a controllable anesthetic, such as ether, which may be lightened as the animal falls into deeper and deeper

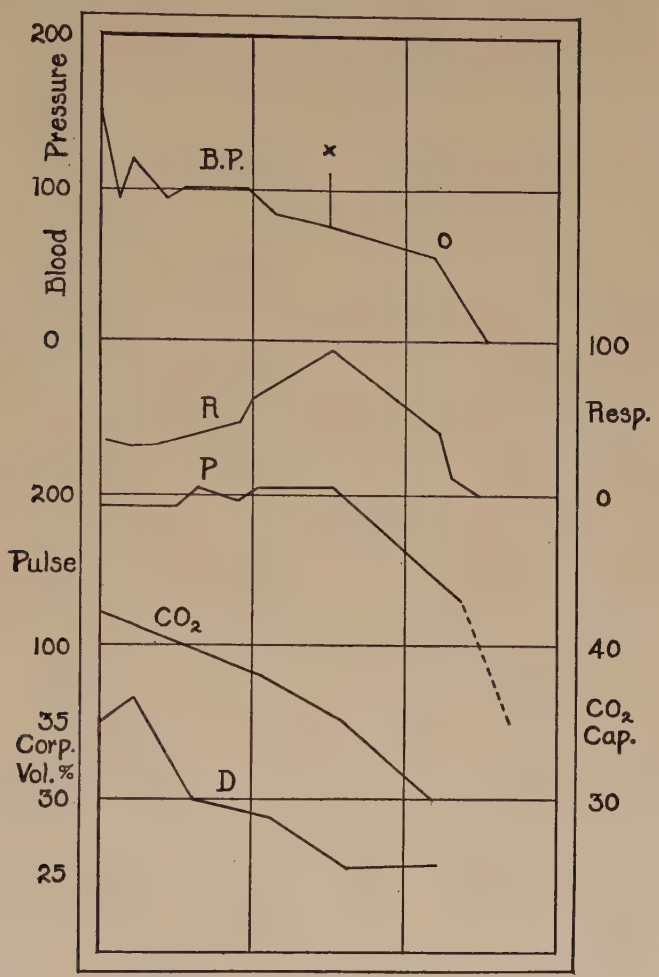

FIG. 13.—RECORD OF CHANGES IN THE BLOOD PRESSURE, RESPIRATION, PULSE AND CO_2 CAPACITY (ALKALI RESERVE) OF THE PLASMA AFTER INJURY OF THE FLEXOR MUSCLES IN THE THIGH. Urethane anesthesia. At *X*, asphyxia caused the rise of blood pressure indicated. At *O*, no rise caused by asphyxia.

insensibility. The lessening of the ether concentration under these circumstances does not improve the circulation.

The fall of pressure after traumatization might be regarded as due to loss of blood and lymph into the damaged tissues, for there is always a considerable swelling of the injured region. This sug-

gestion was tested, however, by removing *post mortem,* with symmetrical cuts, the two hind legs, one normal, the other injured, and weighing them. The difference of weight, which in some in-

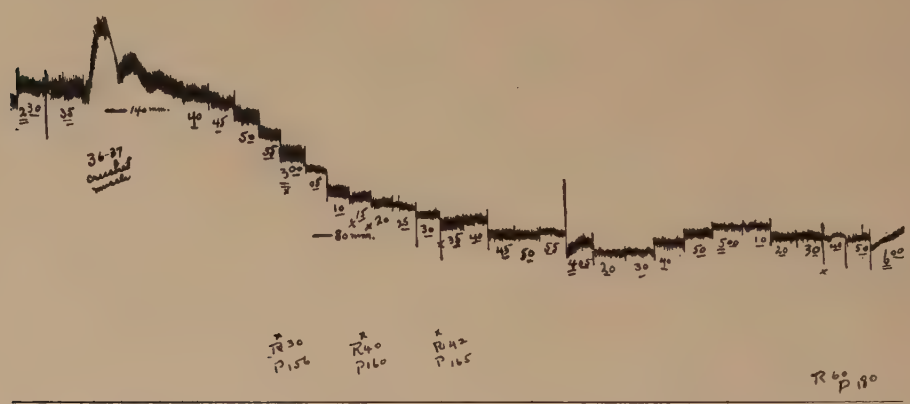

FIG. 14.—TYPICAL FALL OF ARTERIAL BLOOD PRESSURE AFTER CRUSHING MUSCLES OF THE THIGH (AT 2:36–37). *R*, respiration; *P*, pulse.

stances was only 10 per cent of the estimated blood volume, would not represent enough extravasated blood to account for the fall of pressure. It must be admitted, of course, that loss of blood by

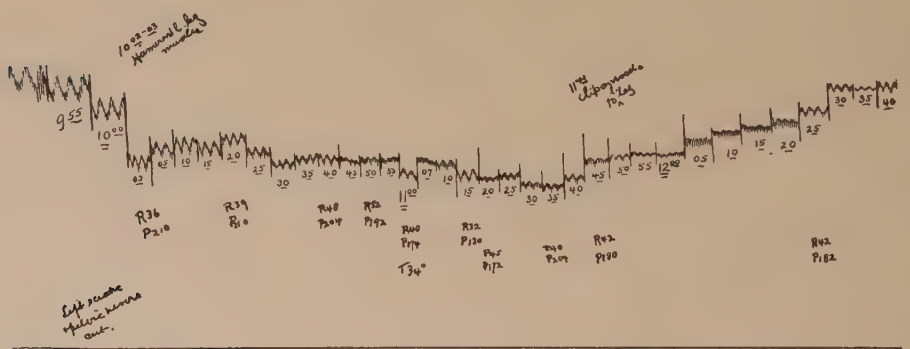

FIG. 15.—FALL OF BLOOD PRESSURE AFTER MUSCLE INJURY (AT 10:02–03) THOUGH THE NERVES TO THE INJURED LIMB HAD BEEN CUT. Rise of blood pressure to the original level after placing a clip (at 11:41) on the blood vessels to and from the injured region.

extravasation, even when slight, may play a rôle in the subsequent development of the low pressure.

The widespread effect in the organism might be due to nervous impulses roused by the trauma. Such impulses, on passing to the

central nervous system, might so affect it as to produce profound depression of nerve cells, or reflex inhibition of the vasoconstrictor center, as has been suggested in theories already considered (see pp. 114–120). Is such the case? The nature of the experiment permits securing evidence on this point. It is only necessary to transect the spinal cord above the lumbar plexus or to sever all nerves of the limb which is to be injured, in order to disconnect the region from the central nervous system. When this has been done and the denervated muscles are traumatized, events occur quite similar to those seen after trauma when the nerves are intact (see Fig. 15). It is clear that there is no essential relation between the production of shock and an excessive stimulation of the central nervous system.

It might be supposed that the local injury, especially when the femur is broken, would permit a sufficient amount of fat to be liberated to cause the pressure to fall. Careful examination was made of the lungs in several instances by the expert pathologists, Louis B. Wilson and Henry W. Cattell, but in no instance was there evidence of any accumulation of fat. Furthermore, there was no twitching, or disturbance of respiration, or other sign which might indicate that fat had passed through the pulmonary capillaries into the central nervous system. The fall of pressure, therefore, cannot be attributed to fat embolism.

Although there was usually a change of respiration in the direction of greater rapidity and lessened amplitude, this was not characteristic of the period immediately after the trauma, but developed as the blood pressure fell. Commonly the respiration became slower toward the end (see Fig. 13). The absence of hyperpnea for some time after the injury, although the CO_2 capacity of the plasma was falling, and the later rapid and shallow breathing, which, as already stated (see p. 131), is not such as to induce a washing out of carbon dioxid from the blood, rule out acapnia as the cause of the lowered blood pressure. This conclusion was confirmed by producing shock by muscle injury, though the breathing was kept uniform by artificial means.

If the low pressure resulting from local trauma is not due to loss of blood into the injured region, or to fat emboli, or acapnia, or to effects on the nervous system, the connection between the general bodily state and the local damage may reasonably be looked for in the remaining great connecting system, the circulation. There may be given off into the flowing blood or lymph, from the damaged

tissue, material which, when carried to the rest of the body, proves toxic and disturbs the vessel walls or their control in such a way as to lower arterial pressure. This idea can readily be tested. The blood vessels of the leg (the iliac artery and vein) are tied, and the muscles then crushed. In the experiment recorded in Fig. 16 the blood vessels of the leg were tied before the muscles were smashed, and the ligatures were left in place for 33 minutes after the trauma. The record shows that there was no drop of blood pressure during this period, although in the cat the arterial pressure usually begins to fall about 20 minutes after the injury. As soon as the blood flow was restored, however, the pressure promptly fell to a low level.

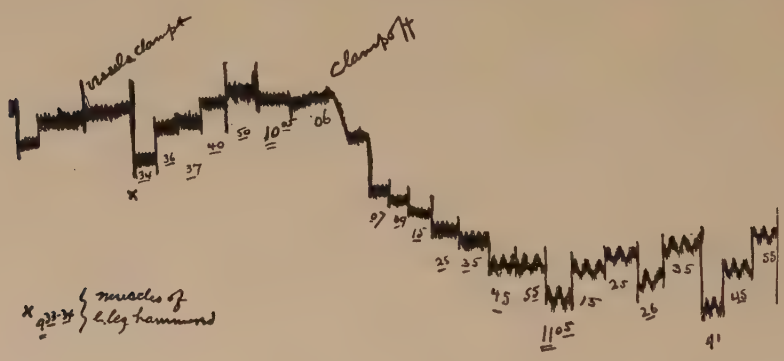

FIG. 16.—FAILURE OF BLOOD PRESSURE TO FALL AT THE USUAL TIME AFTER MUSCLE INJURY IF THE BLOOD VESSELS TO THE INJURED REGION HAVE BEEN TIED. On restoration of the blood flow (at 10:07) the pressure promptly falls.

This phenomenon can be explained on the supposition that a pressure-lowering substance passes from the traumatized region to the rest of the body by way of the circulation when the blood is again allowed to flow. The inference just set forth receives support from experiments in which the muscle was injured and, while the pressure in consequence was falling, the vessels of the leg (the iliac artery and vein) were closed. As shown in Fig. 15, such occlusion of the vessels may be followed by a progressive rise of pressure to the normal level. If the injury is not great, the blood pressure, after falling for a while, may be spontaneously restored. The evidence indicates, therefore, that whatever may be the substance originating

in the damaged tissues, it is fairly promptly changed in the body, or eliminated, so that its effect is not permanent. Further confirmation of the inference that a pressure-lowering material is given off from injured tissue was obtained by massage of the traumatized region. The result was a further drop in pressure. In Fig. 17 is presented the record of blood pressure as it was falling after a smashing of the thigh muscles with fracture of the femur. At the points marked *x* the fragments of the bone were moved in the damaged soft parts. The records taken shortly thereafter showed a greater pressure drop than usual. The practical bearing of these

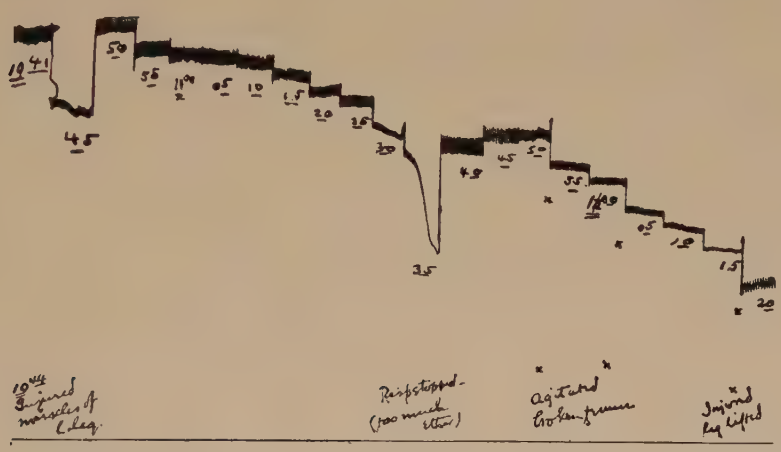

FIG. 17.—INCREASED RATE OF PRESSURE DROP AFTER MUSCLE INJURY, WHEN THE ENDS OF THE BROKEN FEMUR WERE MOVED IN THE DAMAGED TISSUES.

observations on the importance of immobilizing bony fragments is obvious.

Evidence supporting the inference that damaged tissue itself induces shock has been obtained by McIver (personal communication). He established a crossed circulation between two animals, A and B. Thereupon he crushed the muscles of the hind legs in animal A; after an interval varying from 20 to 30 minutes, the blood pressure began to fall in animal B and continued downward until it reached a shock level.

Other experimental work has led to the same conclusion to which Bayliss and I were brought by our experiments. In a recent publication, Turck (5) has declared that the consequences of cell necrosis, brought about in various ways, affect the whole organism in such a manner as to give rise to some of the symptoms

of shock. In June, 1918, he reported experiments (6) on injury to thigh muscles, that were similar to those performed by Bayliss and myself in January and referred to in March and April of that year (7). Unfortunately his experiments were not accompanied by blood-pressure records, and commonly the injection of what he called "shock-toxins" was followed by rapid death of the animal rather than by the production of shock. In November, 1917, Delbet (8), impressed by the similarity between traumatic shock and the shock-like conditions accompanying peritonitis,[1] raised the question whether intoxication did not play a rôle in certain forms of traumatic shock, whether shock was not, in fact, the result of absorption of toxins arising from disorganized and bruised tissues. Delbet and Karajonopoulos (9), in July, 1918, recorded the effects of injecting into guinea pigs and rats the products of autolysis of crushed muscles. They found that these substances were highly toxic, sometimes making animals comatose a few seconds after intraperitoneal injection. Respiration was accelerated, the reaction to noise disappeared, the animal became immobile and in variable time succumbed—effects attributed by Delbet to disturbances of the nervous system. These experiments revealed a toxic substance in muscle autolysates, but it did not produce detailed analogies to the state of shock in human beings. In 1921 Cornioley and Kotzareff (38) reported that muscle injury in guinea pigs and rabbits produced symptoms of shock and commonly, within a few hours, death. These effects could be avoided by placing a tourniquet above the injured region or by prompt removal of the injured member; injection of sterile extracts of injured tissue or the serum from shocked animals induced a shocklike state in the injected animals.

Delbet's view that toxic substances could arise from autolytic disintegration of muscles was questioned by Vallée and Bazy (10), who noted that autolytic ferments of muscles are slow in action. They expressed doubt whether autolysis would result in a toxin sufficiently abundant or active to induce shock, and suggested that bacteria and possibly leukocytes might induce proteolytic changes capable of hastening the production of poisonous material (10, p. 708). It seems unnecessary to assume that tissue

[1] Olivecrona (Acta Chir. Skand., 1922, 54: 559–634) has recently demonstrated numerous resemblances between secondary wound shock and the circulatory failure of peritonitis, in pathogenesis, clinical appearance and vascular changes. Because of these "striking analogies" he assumes that the reduction of blood volume, which he found in peritonitis, is dependent upon essentially the same causes as in shock.

disintegration should be carried far in order to evoke, when injected, a fall of blood pressure. As long ago as 1903, Vincent and Sheen (11) proved that watery extracts of a variety of tissues, when injected into the blood stream, would cause a drop of arterial tension, and Perret (12) in 1909 proved that fluid pressed from raw meat ("myoserum") was highly toxic when injected intravenously.

An Explanation of Traumatic Toxemia.—Explanation of the shock-producing effect of substances which may arise from injured tissue has its beginnings in classic experiments in the history of physiology. Nearly 30 years ago, Heidenhain (13) demonstrated that the injection of "peptone" into the circulation would cause an increased production of lymph, persistent low blood pressure and a notable concentration of the blood. These are changes which Starling (14), in 1894, attributed to increased capillary permeability, especially in the liver.

In 1910 Dale and Laidlaw (15) called attention to a reduction of blood pressure which can be induced by the injection of extremely minute amounts (1 or 2 mgm. per kilo in the anesthetized animal) of histamin, a substance derived from the amino-acid, histidin, by removal of CO_2. Later, attention was called to the shocklike character of the changes which histamin occasions (16). The arteries are constricted (the early constriction of arteries in shock may be due in part to the action of toxic substances), there is oligemia, increased ratio of corpuscles to plasma, and failure of the cardiac output (17). If the chest is opened, the heart is seen beating regularly, but its chambers contain little blood (17, p. 10). The arteries and veins likewise contain little blood. Moreover, by the use of vital red, Dale (17, p. 11) demonstrated that a considerable part of the blood passes out of currency. It appears, therefore, that since the blood is not in arteries and veins, it must be concentrated in capillary areas. Dale reports that the bowel shows a diffuse dusky congestion and that the smallest venules are rendered visible on its surface by their content of dark blood—a condition similar to that observed by Erlanger and his collaborators (see p. 44) in the various forms of shock which they produced. By direct microscopic examination after the injection of histamin, Hooker (18) and also Rich (19) have shown that a large number of capillaries previously not seen become clearly defined because dilated and filled with blood. Dale and Richards (20) have further analyzed the action of histamin. The low pressure resulting from it is not due to relaxation of the

arterioles. It is apparently due to a series of changes in which dilation of the capillaries and pooling of blood within them, poisoning of their endothelial walls so that they are abnormally permeable, escape of plasma through these walls into the tissue spaces, and consequent concentration of the corpuscles (17, p. 12) are the main features. This thickening of the blood would accentuate the tendency for it to gather in the small vessels.

The great significance of these observations by Dale, Laidlaw and Richards is that the action of histamin may reasonably be regarded as typifying the action of a large class of poisonous protein derivatives—products of partial digestion, of bacterial action and of tissue extraction. In 1909 Popielski (21) called attention to the depressor action of organ extracts and showed that "vasodilatins" could be extracted from practically all tissues. In 1911 Barger and Dale (22) proved that histamin was present in the mucosa of the small intestine, in Popielski's "vasodilatin" and also in commercial peptone. Recently Abel and Kubota (23) have adduced evidence that histamin is a widely distributed constituent of animal tissues, organ extracts and enzymatic products, whether derived from animal or vegetable proteins. In all probability, histamin is not the only constituent of tissue extracts and tissue digests capable of lowering blood pressure. Hanke and Koessler (24), for example, have shown that typical peptone shock can be produced by injecting peptone from which histamin is absent. We may follow Dale, therefore, in regarding histamin as a *type* of toxic substance derived from protein material. Although proof is still lacking that a substance histaminlike in character is actually given off into the blood stream when the tissues are severely damaged, the effects of local tissue injury (influencing the rest of the body solely through the circulation) and the effects induced by histamin are so similar that the supposition has a high degree of probability. In both conditions there is a fall of blood pressure. In both there is a reduction of blood volume. In both there is, at least in the early stages, a concentration of the blood (see Fig. 13). And in both, slight hemorrhage results in markedly increasing the shock-like effect. It is a matter of considerable interest that proteolytic bacteria, such as those producing gas gangrene, induce in muscles chemical changes, which, according to Zunz (25), are accompanied by the production of histamin. Extracts of such muscles are highly toxic and rapidly depress the circulation (26). The association of "shock" with gas infection can thus be accounted for.

The view that secondary shock is due to action of toxins arising in injured tissue places it, as Dale (27) has pointed out, in the same general category with anaphylactic shock, for that likewise is probably the consequence of poisoning by protein cleavage products. The shocklike condition produced by toxic substances arising from intestinal obstruction, which Whipple (28) and his collaborators have done so much to elucidate, becomes also closely related to traumatic shock, for chemical study led them to the conclusion that the poisonous agent developed in a closed intestinal loop belongs to the primary proteoses. It is conceivable, furthermore, that the results of methods used by other investigators to produce shock, such as pinching the intestine, as employed by Githens, Kleiner, Meyer and Meltzer (29), or interfering with the circulation, as practiced by Janeway and Ewing (30) and by Erlanger (31) and his group may be accounted for on the basis of a toxin production. Bayliss and I (4) found that after the blood flow had been wholly shut out from the hind limbs for an hour, restoration of the circulation resulted in a sharp fall of blood pressure. And Dale (17, p. 14) proved that if the blood vessels of a fore limb are rendered sensitive to the action of histamin by denervation, letting the blood flow through the hind limbs after it has been shut out for some minutes is followed not only by dilation of the vessels of the hind limbs but also, as in histamin injection, by dilation of the vessels of the sensitized fore limb as well. Since changes in the direction of death and cell disintegration are induced when the circulation is cut off from a region—changes which are accelerated by trauma—the suggestion seems reasonable that the methods mentioned above, used by other investigators to cause shock, likewise involved toxin production.

It should not be supposed that smashed muscle is the sole source of toxic material. Pinching the intestine, as stated above, will induce shock, and I have found that crushing the tips of two or three lobes of the liver may also be effective. Possibly substances given off by extravasated blood are likewise depressive to the circulation: at least, the injection of blood just previous to its coagulation causes a sharp drop of blood pressure.

Clinical Evidence for Traumatic Toxemia.—Aside from the experimental evidence which has resulted in the building up of a theory of traumatic toxemia as a cause of shock there are also clinical observations which extended over approximately the same period as the experimental studies, and which, quite independently, led to the same conclusion. For the clinical studies which developed

and gave support to the theory of toxemia as a cause of secondary wound shock, great credit should be awarded to Quénu, Professor of Clinical Surgery in the Medical Faculty of the University of Paris. As early as 1916, having repeatedly noted in his military service the relation between the occurrence of shock and the attendant gross damage of tissue, he began to suggest to various surgeons in the French army, the desirability of securing clinical data regarding the possible presence of a toxic factor in the production of traumatic shock. In December, 1917, the observations of Rouhier, one of his former internes, were reported by Quénu; and during 1918 a series of papers were presented to the Société de Chirurgie in Paris by Quénu and others—Moulinier, Santy, Marquis, LaCroix, Bertein and Nimier, Rouhier, and Soubeyran—which brought striking confirmation of the ideas which had been expressed. Since an excellent summary of these papers has been made by Quénu (32), it will be unnecessary to report them here in detail. For present purposes a brief outline of the clinical evidence that secondary shock is a traumatic toxemia will suffice.

1. Secondary shock, or what the French call "shock primitif," does not appear immediately after the reception of wounds, as a large number of observers have testified (see pp. 3, 5). Consequently, it is not of the nature of a nervous effect. Furthermore, the state is commonly well established before infection, and therefore is not of bacterial origin.

2. Secondary shock is characteristically observed in association with extensive damage of muscles or with multiple wounds (32, p. 270) scattered over the body. This contention of Quénu is supported by the studies at Béthune (see p. 143) and by the observations of McNee, Sladden and McCartney (33) who described cases in which, without injury to bones or to any vital structure or organ, there was extensive laceration of muscle accompanied by such severe shock that most of the patients died in spite of treatment. In the case of multiple wounds, the large number of small areas of damage would obviously be in sum the equivalent of destruction of a considerable mass in one region. The increase of undetermined nitrogen in the urine and of total nonprotein nitrogen as well as residual nitrogen in the blood of shock cases (see p. 86), may be accounted for as a consequence of the absorption of material from the traumatized area, and also, perhaps, as the effect of tissue damage done by circulating toxins.

3. Everything that favors absorption at the region of injury is favorable to the development of shock. Thus, in observations reported by Quénu (32, p. 270), the development of shock is most severe when the region of damage communicates with the exterior by only a small orifice. The negative aspect of this evidence is presented by cases in which a large fleshy mass, along with the skin which covers it, is carried away by a missile; in such instances shock is slight or wholly absent (32, p. 271).

4. Anything that delays or checks absorption from the injured region delays the development of shock; but if there is a sudden removal of the check, serious results follow. In support of this point Quénu (32, p. 272) cites an incident observed by Rouhier.

A man with a crushed foot was brought in with a tourniquet placed very tight below the knee. The leg was tense, dark colored and full of blood, but there was no sign of shock. Rouhier performed a conservative operation and then removed the tourniquet. Three hours after the operation the patient was in a state of intense shock.

Gregoire (32, p. 272) has reported the analogous case of a lieutenant caught in a dugout after a shell burst. His left thigh was compressed between two logs. Thus he remained for twenty-four hours, alert and guiding the efforts of those who were delivering him. His general condition was good, but he was pale, with a pulse small and rapid and a slightly accelerated respiration. There was no wound; the foot, leg and knee, however, were purplish and cold; above the knee there were two deep hollows formed by the pressure of the logs. Some hours after his rescue the officer became restless and, although treatment for shock was undertaken, he died thirty-two hours after the pressure was removed from the leg. There was no indication of nervous depression and no bleeding in this case. The shock appeared on permitting the circulation to return to the damaged tissue.

Five cases similar to these were reported to me from various surgeons in the hospitals of the American Expeditionary Force in France. One instance was especially striking; a tourniquet had been in place on the upper arm for an uncertain period but the wound in the wrist was so slight that the surgeon proceeded to clean it and take off the compression. The patient was in good condition before the tourniquet was removed. A short time thereafter, however, he went into profound shock and died. It is obvious

that the state developed in these human cases was quite like that developed experimentally by Janeway and Ewing, by Erlanger and his collaborators, and by Bayliss and myself (see p. 153) when a continued low blood pressure was induced by interfering for several hours with the circulation to a considerable part of the body.

The converse of the foregoing observations is seen when, after a very severe wound, the region is isolated by a tourniquet and the limb is amputated proximal to and without removing the tourniquet. Rouhier (32, p. 272) reports a case of this type in which no shock appeared either before or after the operation.

5. Suppression of the injured region, if not too long delayed, causes shock to disappear. Much evidence in support of this statement might be cited. I had occasion to note such cases at Béthune, and Quénu and Rouhier have described in detail instances of the rapid disappearance of shock after cutting away the traumatized tissue (32, p. 273). McNee, Sladden and McCartney (33) have declared that when a quick amputation of a lacerated region is possible "the operation is commonly followed by a remarkable and maintained improvement, so rapid and striking as to appear a direct sequel to the removal of the damaged limb." And they cite the case of a wounded man who was too shocked to allow any movement whatever, and in whom a similar good result was obtained by tying a tourniquet as tightly as possible around the limb which was so badly smashed that amputation was seen to be inevitable if the patient survived. The observations of Santy (32, pp. 233–235) on the effects of delaying operation on the severely wounded, confirm on a larger scale the foregoing individual instances. In a series of 79 cases of non-transportable wounded, in which the time between the reception of the wounds and the surgical treatment was known, the mortality was only 11 per cent when the operation was performed in the first three hours. It rose to 37 per cent when there was delay between three and six hours (though infection is not marked until after six hours), and was 75 per cent in the eighth and ninth hours. These figures vividly illustrate what may reasonably be expected if time is given both for the disintegration of damaged tissue and the absorption of toxic material.

The foregoing experimental and clinical testimony, most of which was gathered only in the last two years of the War, gives a quite new turn to ideas regarding the nature of shock. In this connection the argument of Groeningen (34), written thirty-five

years ago, in support of the nervous origin of shock, is of interest. He pointed out that shock is more frequent after shell wounds and crushing accidents than after cuts and stabs, more frequent with large missiles than with rifle bullets, more frequent with amputations and resections near the trunk than distant from it, more frequent in operations which expose a large, rather than a small surface, and more frequent with a prolonged operation than with a short one. All these considerations he cited as showing that violent stimulation and shattering of nerves are the occasion for shock. It is clear, however, that they may quite as well be instanced as the conditions which are most favorable for causing the death of masses of tissue in the body (thus liberating toxic agents) and for rendering the organism sensitive to the action of such agents.

In the development of theories as to the effects of extensive burns there has been an evolution of ideas similar to that which has occurred with regard to traumatic shock. Forty years ago Sonnenberg (35) attributed death from burns to a reflex depression of vasomotor tone. Modern studies (36) have shown that there is, as in shock, a great increase in the number of erythrocytes, that is, a concentration of the blood, and an enormous mobilization of leukocytes. The suggestion of recent writers (37) is that here too, death, when delayed, is the outcome of an intoxication, probably by protein derivatives set free from the area of tissue destruction. The present outlook seems to be that not only the shock following burns, but also the shock consequent on severe trauma, is properly in the same category with other forms of general depression of bodily functions and defective circulation due to the setting free of toxic material in the body, and that the nervous factors, which for so long a time have been regarded as of primary importance, should be relegated in most cases to a secondary position.

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CHAPTER XX

A CONCEPTION OF THE NATURE OF SHOCK

As a means of summarizing the facts and inferences which have been presented in the foregoing chapters, it seems worth while to attempt to bring together in a general conception the various lines of evidence as to the nature of wound shock. In doing so, I shall try to discriminate, as Gesell (1) has done, between initiating factors and sustaining factors in the complex.

Wound shock occurs as a consequence of physical injury. It is characterized by a low venous pressure, a low, or falling, arterial pressure, a rapid, thready pulse, a diminished blood volume, a normal or increased erythrocyte count and hemoglobin percentage in peripheral blood (thereby differing from simple hemorrhage), a leukocytosis, an increased blood nitrogen, a reduced blood alkali, a lowered metabolism, a subnormal temperature, a cold skin moist with sweat, a pallid or grayish or slightly cyanotic appearance, also by thirst, by shallow and rapid respiration, often by vomiting and restlessness, by anxiety changing usually to mental dullness and by lessened sensitivity. Many of these features may appear at once or as soon after the reception of the wound as observations can be made, or they may develop only after the lapse of several hours.

Initiating Factors in Shock.—The onset of early or primary shock is most reasonably accounted for as a consequence of some disturbance of the nervous system. As the foregoing review of shock theories has shown, it is impossible to eliminate, as a consequence of wounds, a reflex relaxation of blood vessels similar to that which occurs in fainting. Indeed, as Cowell (2) has observed, fainting is in fact not infrequently seen after the reception of wounds. Vincent (3) likewise has seen cases of this character, but in the only instance which he describes in detail (that of a man wounded in the abdomen, who, a few minutes after being hit, manifested the syndrome of shock) the blood pressure at the end of 45 minutes had risen from 60 to 90 mm. Hg. It is possible, then, that

there may be produced by a wound an effect similar in character to fainting or syncope, but persisting for a longer period than the usual fainting spell.

For an explanation of the onset of delayed or secondary shock the theories which have been most commonly advocated in the past, such as inhibition, reduction of the CO_2 content of the blood (acapnia), fat embolism, and exhaustion of nerve centers and certain glands, have all been shown in previous chapters to be inadequate. Their chief and common defect is that they fail to account for the occurrence, both in clinical and experimental shock, of a diminution of blood volume and either a local or a general concentration of blood corpuscles. The group of theories which do take these facts into consideration, namely, those which postulate a primary vasoconstriction with a consequent capillary congestion, fail in that they do not suggest how a vasoconstriction, capable of bringing about a reduction of blood volume would occur.

The theory of secondary shock which has the strongest support both in clinical observations and in laboratory experiments is that of a toxic factor operating to cause an increased permeability of the capillary walls and a consequent reduction of blood volume by escape of plasma into the tissues. Thus the concentration of the corpuscles is also readily explained. It is recognized that after sufficient time has elapsed infection may occur and be of such character in itself as to induce a persistent low blood pressure. According to this theory, there might be no essential difference between the effects of toxins given off by damaged tissue and of toxins resulting from the activity of bacteria.

Emphasis should be laid on the point that toxic agents are usually not working alone to bring about the shock state. Complicating the wounds there is usually some loss of blood. There may have been cold and exposure. Likewise there may have been prolonged lack of food and water. Sweating is a regular accompaniment of severe trauma. All these factors are known to be capable of playing a rôle in producing a more or less permanent reduction of blood pressure. Thus, though 25 per cent of the blood may be lost with no permanent fall of pressure, this loss, when combined with injury, may bring about promptly the signs of wound shock (4). Similarly, after a serious wound with loss of blood, although the state of shock may not be present, ether or chloroform anesthesia and operation may induce a calamitously low pressure. It

is because the state of shock may be the result of a group of circumstances that improvement often follows when one easily controllable factor (for example, cold) is eliminated.

Sustaining Factors.—As has been previously shown (see p. 76), when a low blood pressure is developing in consequence of the action of initiating factors, a critical level is reached below which the metabolic rate of the organism becomes slower. There is diminished heat production so that the body temperature is gradually reduced below normal. Accompanying the lowered metabolism, there is a defective circulation with a consequent defective supply of oxygen. The tissues which are most likely to be damaged because of the anoxemia are those which are most sensitive to oxygen-want, namely, the nervous tissues. Along with this damage, however, there is likely to be, as Krogh (5) has shown, a relaxation of capillaries and perhaps also injury to the capillary endothelium. These injuries to elements which are essential to the maintenance of an efficient circulation, continue the state of shock which has been originated by other factors and may lower still further the already low arterial pressure.

It is probable that a series of vicious circles may thus be started, which, if not interrupted, lead to a still further aggravation of the already existent abnormal state, and which account for the progressive nature of fatal shock. A prominent factor in these vicious circles would be an altered viscosity of the blood. A prime condition influencing the viscosity is the number of corpuscles per unit volume. The polycythemia of cholera, for example, may cause the viscosity to rise from 4.8 to more than 20. Still another agent affecting the blood viscosity to a notable degree is temperature; Denning and Watson (7) found that it was increased 3 per cent with a fall of one degree Centigrade and that the temperature change was more effective the larger the number of corpuscles present. Even in normal persons application of cold increases the red count in cooled capillary areas. All these elements may be regarded as playing a part in the following suggested vicious circles.

1. The retarded blood flow in cooled capillaries would result in a lessened supply of heat to the regions of stasis; the parts would thus become still cooler; the cooling would increase still further the viscosity of the blood, and thereby the blood flow in the capillaries would be still further retarded.

2. Increase in the *number* of corpuscles per cubic millimeter in-

creases the viscosity; thus, the more the blood concentrates in some of the capillaries, the more friction would there be in driving the corpuscles through them, and consequently a still greater accumulation in these capillaries might be expected.

3. As corpuscles accumulate in small veins and capillaries (see p. 41), transudation of plasma through the capillary wall would be favored, and thereby the plasma volume would be reduced.

4. As more blood stagnates in capillary areas, less is returned to the heart; the arterial pressure in consequence continues to fall, the force driving the blood through the capillaries is thereby progressively lessened, and the tendency for blood to gather in these vessels where the passages are narrowest and the friction greatest is continuously augmented.

5. As the blood pressure falls, the "head" normally in the arteries is largely lost and becomes insufficient to maintain the circulation equally in all parts of the body; the blood would be forced through capillaries in which resistance is relatively slight rather than through those in which it is increased; the blood flow in clogged capillaries, as those of the limbs or intestines, would thus tend to be gradually diminished, with resultant greater stasis.

6. As the oxygen supply to capillaries is reduced, they become dilated (5), the capillary area would thus become more capacious and a larger amount of blood could be stored in them instead of being returned to the heart and kept in circulation.

Doubtless there are still other ways by which the abnormal conditions may interact so as gradually to lessen the chances of recovery for the shocked individual. All these deranging processes, however, require appreciable time for their operation. It is obvious that the treatment of shock should be prompt, and directed toward preventing an interplay and a consequent increase of the unfavorable conditions.

Relation of Surgical and Wound Shock.—In the shock sometimes associated with surgical operation, several of the initiating and sustaining factors described above may be present. Among them may be hemorrhage, toxic agents from infection, loss of water from the body by sweating or preparatory purging, and, in addition, anesthesia. Dale (8) has shown that whereas, in the unanesthetized animal, 10 milligrams of histamin per kilo is without lasting influence, etherization with an open mask for two hours (8, p. 16), though not alone effective in causing fall of blood pressure, renders the

animal extremely susceptible to small doses of this typical toxin. In one experiment, 1 mgm. of histamin per kilo given after two hours of ether anesthesia caused a fall of blood pressure from 160 to 33 mm. Hg., and when 2 mgms. had been given, the pressure fell to 26 mm. Hg. Artificial respiration, continued for an hour without ether, then produced no trace of recovery. The blood became much concentrated; the hemoglobin value rose from 75 per cent before injection of the histamin to 118 per cent afterwards. If histamin may be taken as representative of toxic substances given off in consequence of bacterial action or of injury to tissues, it is evident that a general anesthetic such as ether may very greatly increase the sensitiveness of the organism to such substances.

It may be that ether itself acts in such a way as to increase the capillary permeability. Epstein (9) has reported a series of experiments performed under general anesthesia, some with and others without operative interference. In susceptible animals there was a fairly prompt reduction in the blood volume, which he interprets as due to a probable abstraction of fluid from the blood by the tissues. Mann (10) likewise has reported that continued deep etherization, that is, sufficient to lower blood pressure to a considerable degree, for one hour, will by itself cause most of the symptoms of shock to appear. In such instances the pressure usually remains low and is not restored after an hour or two of artificial respiration.

That tissue trauma during operation may liberate toxic material which, in the presence of ether anesthesia, will lower blood pressure, is suggested in an observation by Wallace (11). He has pointed out that two operations involving approximately the same amount of cutting of large nerve trunks and nerve endings in the skin are those of removal of the fore quarter of the body and amputation at the hip joint. In the former operation where the limb is removed along tissue planes and where a relatively small muscular mass is divided, shock is much less likely to occur than in the latter operation where a very large muscular mass is traumatized. Cowell (12) has suggested that the beneficial effect of regional or spinal anesthesia may in such instances be explained in that through complete relaxation the muscle substance is handled and retracted with a minimal amount of bruising and damage.

In surgical operations requiring the opening of the abdominal cavity and exposure and handling of the intestines, there occurs, as

Mann (10, p. 371) has described, an almost immediate dilation of all the arterioles in the exposed area. The splanchnic capillaries and veins are markedly distended, due either to local inhibition of vasomotor tone, or to changes of abdominal pressure, or to venous obstruction, or possibly to all these factors working together. On the whole, the process resembles the first stage of acute inflammation and, indeed, duplicates essentially the phenomena as observed in the classical experiments on that subject. It is evident that here, in a large vascular area with blood vessels close to the surface and normally protected and kept moist and warm by the abdominal wall, there is, on exposure, a sharp change of conditions which is altogether in the direction of such vascular disturbances as our present analysis has proved true for wound shock itself. Abdominal operations may be expected, therefore, to be occasionally accompanied by a shocklike fall of blood pressure.

Although the foregoing consideration of the nature of surgical shock offers suggestions rather than demonstrated facts, the points developed are nevertheless harmonious with all the evidence which we now possess regarding the nature of wound shock. Both in wound shock and in surgical shock, we need more information. We should know the character of the toxic material given off from damaged structures, the amount of damage which needs to be done in order to produce a given amount of this material, and the nature of the damage which produces the largest amount, and the means by which it most injuriously enters the circulation. As Quénu (13) has hinted, quite possibly when we know more of the biochemistry and physiological action of the toxins which induce changes in blood pressure, we may be in a position to treat shock by therapeutic as well as by surgical means. Already an attempt has been made by Cornioley and Kotzareff (13) to immunize animals against shock by previous injection of blood or serum of shocked animals. They admit that their experiments have been too few to yield conclusive evidence, but they regard their results as suggestive of possible protection against the influence of tissue toxins. It is probable, however, that much work will have to be done before we are in a position to profit from these suggestions.

The Inadequacy of the Term "Shock."—The view developed in the foregoing chapters that in shock circulatory failure is due to loss of blood from circulation, though not necessarily from the body, is one which has been gradually developed as experimental

data have accumulated. It is so different from that which probably gave reason for the original use of the term—a sudden collapse due to a severe wound—that a more descriptive term seems needed. The general employment of the word "shock" in an unrelated variety of meanings, as, for example, emotional shock, shell shock, concussion shock, besides traumatic, surgical or toxic shock, points likewise to the need of a new designation. This need has been recognized by several recent workers. Quénu (14, p. 297) has proposed the term "depressant syndrome" as one which combines a designation of the essential features of shock—the weakness of the heart, slow circulation and the depression of the nervous system. Kermission (15) proposed the term "traumatic toxemia," but, as Quénu has remarked, it is too vague and inexact; traumatic toxemia is not always expressed in symptoms of shock—there may be traumatic intoxication of a grave character which has nothing to do with that syndrome. Gesell (1, p. 498) whose work called attention to the slow flow of blood which precedes the fall of blood pressure in shock, has offered the term "traumatic hypodromia" as one sufficiently general to meet all conditions and yet specific enough to be of definitive value. In 1918, I suggested that the word "exemia" might be used (16). It was employed by Hippocrates and signifies "drained of blood." As the foregoing discussion has shown, such is the state of the shocked man—his blood pressure is low because essential parts of his circulatory apparatus have been drained of blood. The term "exemia" may properly be used, therefore, to describe this condition. The word is short and readily adaptable as a descriptive term to different aspects or occasions for hypotension, as hemorrhagic, toxic, or traumatic exemia.

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CHAPTER XXI

THE TREATMENT OF SHOCK

In the following suggestions for the treatment of patients who are suffering from shock, or who, severely injured, may pass into a state of shock, the facts which have been developed in the foregoing chapters, and to some degree also the theoretical considerations which have substantial support, will be applied. It is well to keep in mind at the outset that the *early* use of *simple* measures is of primary importance. Such measures will be described in relation to the conditions which have to be met in the course of treatment.

Hemorrhage.—The evidence already given proves that bleeding may sensitize the organism to factors which are likely to induce shock and that individuals who have been severely injured, and are in an unstable condition therefrom, may be reduced to shock by relatively slight hemorrhage (see pp. 37, 95, 152). Furthermore, in association with serious wounds, there is likely to be a considerable loss of blood and therefore urgent need that no more be lost. All these conditions strongly emphasize the importance of employing measures which will prevent a further bleeding that may be of critical importance to the life of the individual.

The readiest method of checking hemorrhage when a limb has been wounded is through the application of a tourniquet, and there is usually strong temptation to apply it promptly. Cases have been cited (see p. 155) in which long exclusion of the circulation from a part of the body will result in the production of shock when the blood flow is restored to the anemic part. These instances illustrate a definite danger which may arise if a tourniquet is used to control hemorrhage and consideration is not given to how long it has been in place. The evils of thoughtless and indiscriminate use of the tourniquet became so prominent that in certain parts of the British army this method of hemostasis was definitely discouraged. Medical officers then found that in most cases the flow of blood could be stanched by applying compression to the wound itself. The advice of Wallace and Fraser (1), who had a vast experience with shock cases during the War, is as follows:

Bleeding is to be arrested by pressure upon, or ligature of the bleeding point itself and not by constriction of the limb above or by tying the artery on the proximal side of the injury. The systematic use of the elastic tourniquet should be limited, and its use, apart from during an operation, should be restricted to those cases in which a limb is completely smashed or blown away, or as a temporary measure while a patient is being carried to a regimental aid post. If the medical officer finds that a tourniquet has been already applied, it is his duty to remove it at once and to examine the limb so as to ascertain whether there is actually hemorrhage, and, if so, to take measures for its arrest.

A rule which is generally applicable is that the tourniquet should be avoided altogether if possible and that if one is absolutely required it should be placed as far from the trunk as conditions permit and removed as soon as vessels are tied or snapped. If it must be left long in position a note should be attached to it stating when it was applied.

The suggestion has been offered (2) (3) that if a limb has been so badly mangled that it cannot be saved, a tourniquet should be set close above the traumatized tissues and left in place *until after amputation.* The amputation should be performed proximal to the tourniquet. Thus, throughout the period of transportation and preparation for removal of the limb, the body is protected against toxic material which is present in the torn and smashed tissues and is likely to be absorbed.

Loss of Body Heat.—The well established association between the incidence of shock and loss of body heat, emphasizes the urgency of taking every precaution to conserve the store of heat which the body has and to give back to the body the heat which may have been lost. In accordance with this observed relationship, the following principles of treatment should be applied.

When an injured man is being examined, he should be subjected to as little exposure of the body as possible; only one part should be exposed at a time and it should be promptly covered again. These precautions are especially necessary in cold weather. If the patient cannot promptly be placed in bed, he should be wrapped with blankets. Whether the patient is lying on the ground or on a stretcher, *more* blankets, if available, are needed *under* the body than over. The reason for this is that the blanket protects against heat loss by the air which it holds enmeshed in its fibers. The weight of the body lessens the air space in the fabric and consequently reduces the amount of protection. Under military conditions it is necessary to reduce the number of

blankets to a minimum. By using the method illustrated in Fig. 18, three blankets may be made to provide four layers above and four below the patient. Of course the feet should be wrapped in warm covers.

If the patient is already cold or is likely to lose heat in spite of blanketing, heat may be contributed to his body by means of hot water bottles. Great care should be exercised to avoid a degree of heat which might cause burns. The bottles are more effectively employed if both sides instead of one are brought into contact with the body. Further, heat passes faster from a warm to a cold object than to a lukewarm object. And, finally, heat is distributed throughout the body by the circulating blood. In accordance with these considerations one hot water bottle should be laid on the abdomen, and the hands, which are likely to be cold, placed over it. The second bottle should be placed between

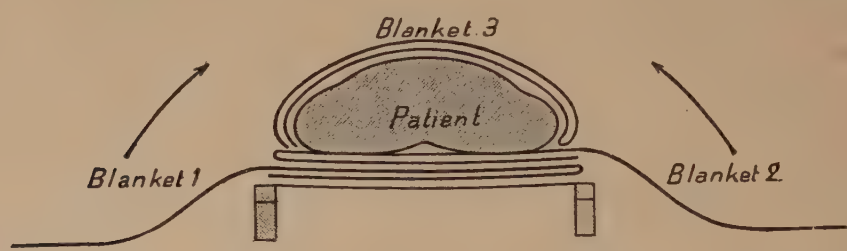

FIG. 18.—METHOD OF FOLDING THREE BLANKETS TO PROVIDE FOUR LAYERS BENEATH AND FOUR LAYERS ABOVE THE PATIENT. The outer ends of blankets 1 and 2 are folded over the two layers of blanket 3 already in place above the patient. (From the pamphlet, *Traumatic Shock and Hemorrhage*, issued from the Division of Surgical Research, Central Medical Department Laboratory, Dijon, and published by the American Red Cross for the American Expeditionary Force, France, 1918; after Cowell.)

the feet, which also are likely to be cold. If more bottles are available they should be placed between the thighs or pushed towards the axilla between the arm and chest on either side. By such a distribution, the heat passes chiefly to the body rather than in large part to the layer of air in the surrounding blankets, and, furthermore, it warms the parts which are most likely to be, or to become, chilled when the circulation is poor.

Another highly effective mode of contributing heat to the body is by means of hot drinks. There are, however, limitations to the use of this method; for in case of injury to the alimentary tract the taking of fluid would be likely to wash material into the peritoneal cavity, and besides, fluid taken by mouth is sometimes not retained by the severely wounded. If the gastro-intestinal canal has not been opened by injury and if the swallowed fluid is not vomited, a

hot drink is by far the best method of warming. All of the heat in it, above the temperature of the body, passes to the body itself. Moreover, the fluid helps to restore a reduced blood volume. It also satisfies the distressing thirst which is so constantly complained of by the wounded. The hot drink may be given in forms which are relished, such as hot tea or coffee. Under military conditions these drinks may be provided at advanced stations and may be given repeatedly, when they are tolerated, in the course of the journey to a permanent hospital.

Preliminary dressing of wounds should be done, if possible, in a warm place. In civil surgical practice, the injured man can often be taken directly to a hospital. In military activities, however, this is a rare possibility, and provisions should be made in advanced dressing stations for keeping the patient warm during the first care of his wounds. An arrangement which has proved simple and satisfactory in military service is that of providing in these stations a rectangular support, the length and width of a stretcher and about 3 feet high, which is surrounded by blankets and heated by a lamp or oil stove placed on the floor. Over this warm chamber stretchers may be set and patients thus kept warm during the examination of their wounds.

Already, in previous discussion, attention has been called to the rapid loss of heat through wet clothing (see p. 92). During the preliminary dressing outer clothing which is wet should be removed and replaced by more blankets. If the patient can be kept warm, however, this need not be done.

During the War, an important improvement in the care of the wounded, especially in cold weather, was made when devices for warming the motor ambulances were installed. Some accidents occurred from escape of gases into the car when the exhaust was used to supply the heat. Cars may be heated, however, by hot water from the radiator.

When, on arrival at the hospital, the patient has a low temperature and cold skin, his clothing should be promptly removed or cut away (with care not to lose more heat) and he should be put in a warm bed. A highly effective means of warming the patient while in bed is to set over him fracture frames, which are covered with blankets, and then to introduce heat into the covered space. If electricity is available, a permanent arrangement for this purpose may be made by wiring six or eight electric lights so that they

project inward from the frame. Another device which may be used in the absence of electricity is that of leading from near the floor to the space under the fracture frames, an elbowed stove pipe and using as a source of heat a lamp or alcohol burner set on the floor under the lower end of the pipe. It is advisable to pass the pipe through a wooden board, shaped like the end of the frame, so as to avoid danger of burning the bedclothes.

Great care should be exercised not to overdo the heating. A shocked man is suffering from reduced blood volume and should not be made to lose unnecessarily more fluid from his body by sweating.

The clinical improvement seen when a wounded man, cold and shocked, is merely put to bed and warmed is often astonishing. The pulse, absent at the wrist, may return in good volume, and within an hour as the patient becomes warm the blood pressure may rise to a satisfactory level.

Pain and Restlessness.—Evidence already presented (see p. 149) has shown that the agitation of a broken bone in damaged tissue results in a sharp fall of blood pressure—an effect which may be accounted for by the further traumatization of the tissue and by the liberation of more toxic material. Experience during the years of the War proved to British surgeons that the use of the Thomas splint while bringing in the wounded did more, perhaps, than any other agent to reduce the incidence of shock. The lesson of these facts is that when in a serious injury a bone is broken it should be carefully splinted before moving the patient. This precaution is especially important in fracture of the femur, with the possibility of damage to the large muscle masses which surround the bony fragments. The benefits of splinting rise both from lessening the occasion for pain and from minimizing further destruction of the soft parts by movement of the broken bone.

When the conveyance of a severely wounded or shocked man is likely to last for a considerable period and to involve a good deal of agitation and jarring, as is the case in military operations, his chances, unless infection is developing rapidly, are improved by stopping occasionally and giving him opportunity to be warmed, rested and supplied with fluid. Opportunities of this character are usually offered in warfare at the regimental aid post and the advanced or ambulance dressing station before the hospital is reached. Commonly the ambulance service is eager to make a

record for rapid transportation of the wounded. This attitude should be tempered by the judgment of the surgeons, who should not permit the seriously wounded to be rushed to the next station before showing the improvement which arises from warmth and rest.

Concerning the use of morphin, there have been differences of opinion. It has been given to badly wounded men hypodermically even in as large a dose as one grain. Crile and Lower (4) have advocated giving the drug to the point at which the respiration sinks to at least 12 per minute. On the other hand Marshall (5), who has had very large experience in anesthetizing shocked men, has testified that the severely wounded, when deeply morphinized, make an unsatisfactory recovery after operation. The object to be sought in giving morphin is to blunt the feeling of pain and to lessen anxiety, especially during a rough and dangerous carry, and besides, to reduce or abolish the restlessness which is wasting the patient's energy and making a greater demand on his defective circulation (see p. 74). As experiments have proved (see p. 71), after morphin the blood pressure may be lowered further without producing acidosis than is possible otherwise, an observation which suggests that morphin lessens metabolism at a time when the oxygen, needed for the maintenance of chemical changes in the cells, is likely to be insufficient. The drug should be given, therefore, until the patient is comfortable and quiet. In some cases ¼ grain may be sufficient, in others ½ grain may be needed. The dose should be repeated if necessary.

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CHAPTER XXII

THE TREATMENT OF SHOCK (*Continued*)

THE LOW BLOOD PRESSURE

If simple measures such as warmth and rest do not result in producing a rise of systolic pressure to at least 80 mm. Hg. fairly promptly, other means should be used to raise it. Evidence of extensive hemorrhage associated with a very low blood pressure would warrant radical interference as soon as the patient is warm. The decisively harmful effects of prolonged insufficient volume-flow of blood, which have been emphasized in previous chapters, should always be kept in mind.

To rationalize the treatment of low pressure, the facts already developed in earlier discussion should be applied. It should be remembered that the blood is serviceable to the tissues only as it flows through the capillary region, and that the prime cause of the low pressure in shock is a diminished volume of blood in circulation, and, further, that apparently the stagnant blood is not in the arteries nor in the veins, but is concentrated in capillary areas. With these considerations in mind, we may regard critically the proposals which have been made for improving the circulation.

Posture.—For many years, in civil hospitals, shock cases have been treated by raising the foot of the bed so as to permit gravity to aid the return of blood from the large veins of the abdomen to the heart. There is some evidence that in normal individuals the blood pressure in the head-down position may be increased approximately 15 mm. Hg. over the figure for the supine position (1). Recently, Henderson and Haggard (2) have questioned earlier results because in the cases studied by them the change from the flat to the inverted position was accompanied by no marked effect upon either systolic or diastolic pressure. The pressures rose about as often as they fell, due probably to the slowing of the heartbeat which accompanied the inversion of the body. Even in normal men, therefore, it is questionable whether a greater height of pressure

is developed in the arteries when a head-down position is taken. At Béthune observations were made on the effects of raising the foot of the bed in cases of shock, but no benefit was noted as a result of the procedure. On the other hand, it proved to be rather disturbing to the patient. The failure of any benefit from tilting the bed is made rational by the facts which have already been presented. The method was based on the assumption that the stagnant blood was in the large veins of the abdomen. For gravity to be effective the blood would have to be chiefly in the vena cava, for there is no evidence that the blood of the portal vein can be made to pass through the liver capillaries by gravity drainage. All the evidence, both clinical and experimental, proves that the stagnant blood is not in the large veins in secondary shock (see p. 39). Consequently the attempt to improve the circulation by postural change is not likely to have an important influence. In primary shock it may be more serviceable.

Vasoconstrictor Drugs.—For many years it has been the practice to attempt to improve the circulation in shock through the administration of adrenalin or pituitrin. Adrenalin constricts the arterioles in so far as they are effectively innervated by the sympathetic. Pituitrin acts by constriction of smooth muscle of the arterioles everywhere and has a more lasting effect than adrenalin. No doubt the arterial pressure may be temporarily raised by the intravenous exhibition of these drugs. The rise of pressure, however, results from increase of resistance in the tips of the arterial tree. In consequence the blood accumulates more and more in the arteries because of the difficulty of exit. This accumulation will lead to a temporarily better flow through the heart muscle and the cerebral vessels when adrenalin is used, because in the presence of a high arterial pressure the arterioles of these regions are not constricted. The effect, however, is very temporary. When pituitrin is used there may be contraction of the smooth muscle of the cerebral as well as the cardiac vessels. The increased arterial pressure, however, when either of these drugs is employed, gives a wholly spurious impression of the state of the circulation. Damming the blood in the arterial portion of the circulatory system, when the organism is suffering primarily from a diminished quantity of blood, obviously does not improve the volume-flow in the *capillaries;* in other words, merely a higher arterial pressure is not the desideratum in the treatment of shock, but a higher pressure which

provides an increased nutritive flow *through the capillaries all over the body.* This can be obtained when, as in shock, a diminished volume-flow is the cause of the low pressure, only by increase of the volume-flow. It cannot be accomplished by medication. In British and American services the use of stimulant drugs, such as strychnin, and also vasoconstrictor drugs, such as pituitrin and adrenalin, practically disappeared during the course of the recent War.

Various other combinations of drugs have been suggested. Descomps and Clermonthe (3) went so far as to make intravenous injections of Hedon's fluid (a hypertonic solution containing the chlorids of sodium, calcium and potassium, sodium bicarbonate and phosphate, and magnesium sulphate) to which they added soluble extracts of hypophysis, thyroid and adrenal glands, testicle and spleen, and also strychnin sulphate, and crystallized digitalin, and they proposed adding camphor. The theory of this conglomeration was that the function of the sympathetic system was dependent upon the activity of the endocrine glands, which they assumed to be deficient in shock, and they report that in eight cases the pulse became more regular in 6 or 8 hours and the arterial pressure rose. This extraordinary mixture has not been widely used, and, for reasons given above, seems to have no defensible place in the therapy of shock.

A drug which has been advocated for shock cases, especially by some French surgeons, is camphorated oil injected slowly into the circulation itself (4). The argument for this drug is that it promptly improves the action of the heart and thus permits time to be gained for the use of other measures. Here again we may apply critically the evidence obtained in clinical and experimental observations. It has shown that the heart is not primarily affected in shock (see p. 28). Unless the low pressure has persisted for a long time, the action of the heart promptly becomes normal as soon as a sufficient volume-flow of blood is present for it to act upon.

Forced Absorption of Fluids.—Gesell's experiments proved that a relatively small loss of blood greatly reduces the volume-flow through peripheral organs (see p. 49). The converse is also true; when the circulation is failing from a low content of the vessels, slight increase of blood volume will greatly increase the peripheral flow. This fact is the basis for treating low blood pressure by increasing the circulating fluid even though solutions incapable of conveying oxygen or carbon dioxid are employed for that purpose.

As Gesell (5) has pointed out, the nutrient flow may be increased several hundred per cent by injecting an inert solution—an increase out of all proportion to the dilution of the blood produced by the added fluid. According to Rous and Wilson (6), about 75 per cent of the total hemoglobin may be safely removed, provided the bulk of circulating fluid is maintained.

The simplest means of increasing a reduced blood volume, if the condition of the patient is not urgent, is by giving fluids by mouth. Unfortunately, vomiting is likely to occur when shock is well developed. In that event, and in case the patient's condition will permit, the rectal route may be used. Robertson and Bock (7) have proved that in cases of reduced blood volume, fluid administered in large amounts by way of the alimentary tract is to a high degree retained in the circulation. By direct tests they showed that, when patients who had suffered hemorrhage were treated by forcing fluid through the intestinal wall into the circulation, the blood volume could be much increased. They gave water by mouth as rapidly as the patient would take it, and normal salt solution by rectum; after well marked hemorrhage 250 c.c. of normal salt solution (7, p. 239) could thus be given every half hour. By these procedures in one instance they increased the blood volume nearly 1400 c.c. in 24 hours (7, p. 234). As the volume became restored to near the normal, the urine output became almost as large as the water intake. These observations on cases of hemorrhage are an indication of what may be done through simple measures in non-urgent cases of shock, where there is a similar lack of circulating blood. The remarkable feature of Robertson and Bock's results is the increased volume of fluid held in the blood vessels when water or salt solution enters the body by natural channels, which is very different from the effects of direct injection.

Injection of Salt Solutions.—All the evidence, both clinical and experimental (8), indicates that the intravenous injection of warm normal salt or Ringer's solution has only a temporary effect. The injected fluid promptly passes from the capillaries into the tissue spaces and within a brief period the pressure is as low as before, if not lower (see Fig. 19).

Favorable results have been claimed for normal salt solution given subcutaneously, but not on the basis of critical observation. Both in human cases and in experimental animals with low blood pressure and sluggish blood flow, salt solution injected under the skin has been found

post mortem spread through the fascia in the region of injection. At Dijon, Robertson carefully followed the hemoglobin percentage after subcutaneous injection of salt solution in a shocked animal and found no dilution of the blood such as would appear if the solution entered or were retained in the vascular system.

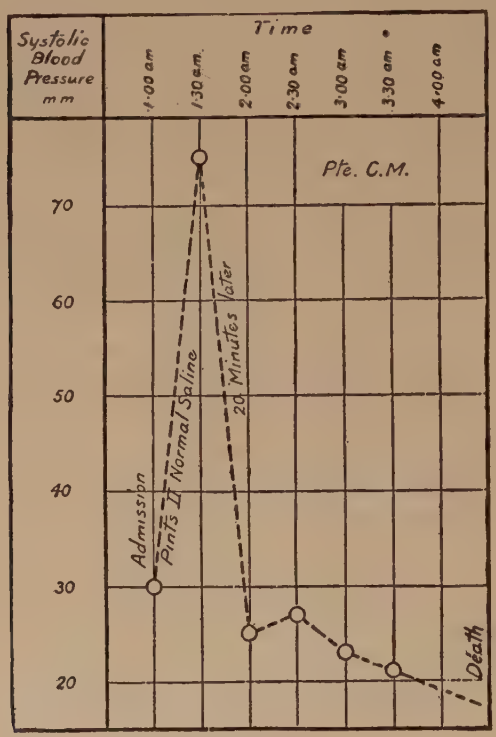

FIG. 19.

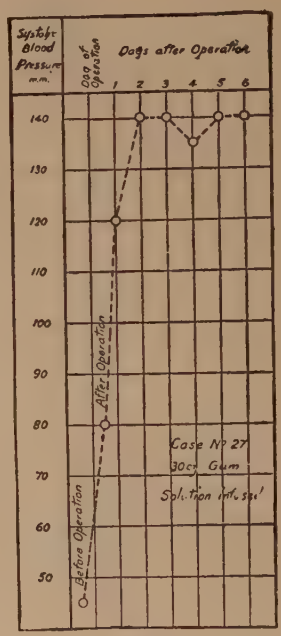

FIG. 20.

FIG. 19.—CASE OF SIMPLE FRACTURE OF RIGHT HUMERUS AND SHELL WOUND INVOLVING RIGHT KNEE. Two pints of normal salt solution administered intravenously on admission; immediate rise of systolic pressure to 75 mm., but within an hour a fall to a lower level than before (from Fraser and Cowell).

FIG. 20.—CASE OF ABDOMINAL SHELL WOUND APPARENTLY MORIBUND ON ADMISSION. At operation, two pints of blood found in the peritoneal cavity. Six perforations of the intestine were sutured. Intravenous injection of gum-salt solution during operation (thirty minutes); blood pressure, 80 mm. Hg. and fair pulse. Next day blood pressure, 120 mm., and later 140 mm., where it continued (from Fraser and Cowell).

Early in 1917 (9) the injection of hypertonic salt solution was suggested as a way of withdrawing fluid from the tissues and increasing the blood volume by an "internal transfusion." Experience proved, however, that, though the pressure could thus be raised, the effect was transitory (10). No doubt the higher osmotic pressure of a concentrated solution does for a time attract water into the blood stream, but

since the capillary wall is freely permeable to salts, they are soon equally distributed and then nothing prevents a rapid filtration of the injected fluid outwards into perivascular spaces.

Because of the strikingly favorable immediate results obtained by injecting sodium bicarbonate in shock cases which were characterized by marked "acidosis" and "air hunger," Wright (11) and later Frazer, Cowell and I (12) suggested that such solutions be employed to raise the blood pressure and simultaneously to increase the low alkali reserve. Clinical experience proved, however, that usually by the time such extreme conditions have developed, sensitive structures in the body have been so much injured that the beneficial effects are not likely to be permanent; and experimental analysis led to the conclusions that the reduced alkali reserve is the consequence of a low blood pressure (see p. 63) and that it is probably not an important secondary factor in augmenting shock (see p. 128). Since "acidosis" in shock indicates a deficient delivery of oxygen to active tissues, the rational move is not to treat the effect, but the cause, that is, to provide for a better supply of oxygen by early and permanent improvement of the circulation. As the foregoing paragraphs show, salt solutions alone are incapable of achieving this result.

Gum-salt Solution.—Salt solutions fail to produce a permanent rise of blood pressure because they lack a colloidal material which, like the protein of the blood plasma, will not pass through the capillary walls, and which by its osmotic pressure prevents water from passing through. Various colloids have been suggested to compensate for this lack—among them boiled starch, agar, dextrin, gelatin and gum acacia. Bayliss (8, pp. 75–91) has carefully analyzed the properties of these substances, and has found that gum acacia alone is free from serious objection and capable of replacing blood plasma. A solution of 6 to 7 per cent of it in 0.9 per cent sodium chlorid has the same viscosity as whole blood and the same osmotic pressure as blood plasma. It is chemically inert; it does not cause thrombosis or promote clotting; it can be sterilized without chemical or physical alteration; and it does not induce anaphylactic reactions when repeatedly injected. Emphasis should be laid on the necessity of using for the solution the purest pearls of gum acacia. They should be placed in tap water or *freshly* distilled water and allowed to swell for a day. They may then be dissolved quickly over a water bath. The solution must be filtered finally through paper of coarse texture. Bayliss (8, p. 97) has shown experimentally that "gum-salt" solution will restore permanently a low blood pressure

produced by removal of 40 per cent of the estimated blood volume. Meek and Gasser (13) have reported injecting the solution until it was 10 per cent of the blood, without ill effects. And Drummond and Taylor (10, pp. 136, 137), after an experience with it in 38 cases, and McNee, after an experience in more than 100 cases, have declared it harmless for man. Farrar (25) has used the solution in numerous cases with no bad results, indeed with results quite favorable to establishing its utility and value. Its effect in building up a satisfactory blood pressure is illustrated in Fig. 20.

Though reports highly favorable to the use of gum-salt solution have been made (10), strong opinions have been expressed against its use. Mixter (14) has cited two cases in which death was, in his opinion, caused or hastened by gum-salt injection, and R. I. Lee (15), though reporting an excellent result from its use, mentions two cases of collapse. A case of death following use of the solution has been described by Olivcrona (26), and two deaths attributed to it have been described by R. V. A. Lee (27). I have earnestly endeavored to obtain reliable data showing under what conditions the solution is useless or harmful. In October, 1918, at my suggestion, Major O. H. Robertson visited the forward hospitals in the American area and systematically collected observations and opinions from a large number of resuscitation teams. Along with laudatory statements there were some that were indifferent and others condemnatory. According to Robertson's analysis, the unsatisfactory results occurred in cases of long-lasting shock (15 to 20 hours), cases treated before being warmed, cases of very severe hemorrhage, and cases of gas bacillus infections (16). These conclusions coincide with those of Ohler (17, p. 852) who had large experience as a resuscitation officer.

Both in the British and in the American armies, gum-salt, when used *early* in cases of shock and moderate hemorrhage, had excellent effects which brought forth enthusiastic commendation from good clinical observers. These results were comparable with those obtained under experimental conditions on lower animals. But during September and October, 1918, when the wounded were brought in after prolonged exposure to cold and wet, the favorable action of the solution, that had been noted in July and August when the weather was warm and the transportation prompt, were no longer observed. American medical officers reported that they tried it then and obtained no benefits from it. Under the hard conditions of the autumn, however, it was found that blood transfusion also was often quite as ineffective as the artificial fluid in restoring the circulation. British experience was summarized

in a statement issued after a conference of British surgeons (including Major General Sir Anthony Bowlby, Major General Sir Cuthbert Wallace, Colonels S. L. Cummins and T. R. Elliot, Majors J. W. NcNee and Geoffrey Marshall and Captain N. M. Keith) held in November, 1918. They agreed that when made from pure pearls of acacia and introduced warm and at a slow rate, gum-salt solution has no seriously harmful effects; that it has a valuable place in resuscitation; but that in order to have beneficial action it must be given *early*.

I have occasionally seen "chills" follow its use in cases near death from shock, but a similar reaction occurs, at times, after the intravenous injection of blood or normal salt solution. In this connection the recent discovery of Stokes and Busman (18) is important. They found that just such reactions as have been ascribed to gum-salt—chills, sweating and subsequent prostration—are due to a toxic agent present in certain varieties of new rubber tubing which they used for intravenous injection. This factor should be ruled out before evil action is attributed to the gum-salt solution itself. De Kruif (19) has subjected gum-salt solution to very thorough tests as to its toxicity, with negative results. All the *experimental* testimony indicates that the properly prepared solution is innocuous.

Various reports mentioned above have emphasized the importance of early treatment of a low blood pressure. Reasons for this have already been discussed in relation to the damage done to nerve cells when long subjected to oxygen-lack (see p. 98). In addition, there is likely to be, as a consequence of defective blood supply and also of the action of toxic agents, an increasing permeability of the capillaries (see p. 44). Keith (20) reports two cases in which 1,000 c.c. of gum-salt solution were injected, but without beneficial effect. In one case determination of the blood volume before and one hour after the injection (shortly before death) showed that the addition of 1,000 c.c. had increased the blood volume only 200 c.c. In the other case, gum-salt solution was given after the blood had concentrated so that the hemoglobin percentage had risen from 104 to 120. The injection caused no improvement, and at autopsy the lungs and subcutaneous tissues were edematous. Similar instances have been reported to me by resuscitation officers in the American army. The conclusion drawn by Keith was that in the late stages of shock the capillaries may become so damaged that they are no longer capable of retaining fluid, even though it be a colloidal solution (20, p. 15). These observations and the inference from them

fit closely the conception that in shock the reduction of blood volume is due to escape of plasma because of increased capillary permeability.

Hypertonic Gum Acacia and Glucose.—Erlanger and Gasser (21) have produced shock experimentally by a standard procedure—holding the arterial pressure down to 40 mm. Hg. for two and a quarter hours. They have then treated the animals by giving 25 per cent gum in 18 per cent glucose. The virtues of this hypertonic solution they believed to be (*a*) the drawing of fluid from the tissues into the blood stream and thus the increasing of blood volume; (*b*) the maintenance of the increased volume through some property of the gum acacia; (*c*) the dilation of the arterioles through a specific action of the hypertonic glucose; (*d*) the increase of the energy and food supply of the heart; and (*e*) the augmentation of metabolism (21, p. 419). When animals subjected to standard shock-producing trauma were left untreated (23 cases), 48 per cent died within 48 hours. When they were treated (21 cases) by injecting intravenously the hypertonic solution at the rate of 5 c.c. per kilogram per hour, only 24 per cent died within 48 hours (21, p. 396).

There is some question whether in this particular feature results obtained on the shocked dog can be justifiably transferred directly to man. For example, the dog does not absolutely lose fluid from the body by sweating as man does; it is probably present in the tissues or lymph spaces. On the other hand, in wounded men, according to Robertson and Bock (7, p. 233), blood volume is made up very slowly; often after 5 or 6 days these cases have less than two-thirds of the normal. The indications seem to point, therefore, to the need of adding fluid to the body rather than attempting to withdraw fluid from tissues which may themselves be lacking it. Erlanger and Gasser (21, p. 420) have tested their method, however, on shocklike states in man (12 cases) and they found that the solution was not only innocuous, but produced results "strongly suggestive, to say the least, of beneficial action." The only ill effects which they observed occurred under experimental conditions when the hypertonic gum solution was run rapidly into the veins of dogs almost moribund; then the heart became irregular and stopped as though it had passed into fibrillation. After an experience with over 200 animals, they state (21, p. 397), "If there is any one thing we are convinced of, it is that gum acacia when given slowly is entirely innocuous."

Full knowledge of the merits and limitations of gum-salt solution[1]

[1] For a discussion of the evidence for and against the use of gum-salt solution, see Bayliss: Journ. Am. Med. Assoc., 1922, 77:1885.

under clinical conditions may be regarded as not yet attained—except in late shock, when it has proved useless. After severe induced hemorrhage and in experimental shock caused by muscle injury, gum-salt solution has been shown to be capable of raising and maintaining a normal blood pressure. Its service under these circumstances lies in speeding the circulation and thus inducing a greater use of the red corpuscles for the delivery of oxygen to the needy tissues. At best, however, it is only a substitute for blood.

Transfusion of Blood.—The transfusion of compatible blood in cases of persistent low arterial pressure has been proved beyond question, by experience during the War, to be highly valuable. Blood can permanently raise arterial pressure, as gum-salt solution can; but in addition it contributes to the recipient a large increase of oxygen-carriers—the red corpuscles. Theoretically, however, in pure shock, when plasma has escaped and corpuscles are crowded in capillaries, gum-salt solution should be quite as good as blood, if not preferable to it; and even after hemorrhage, when not severe, it should serve well. In his series of carefully observed cases, Keith found that the results of intravenous injection of gum-salt solution and whole blood were practically identical (20, p. 14). He concludes that probably in some cases of shock, blood transfusion would give better results than the solution, but such cases did not come under his observation. On the other hand, Robertson and Bock (7, p. 242) and Lee (15) declare that when the hemorrhage factor is large in the production of circulatory deficiency, blood is highly preferable to any indifferent fluid. Ohler (17, p. 848) is of the same opinion, and he cites cases in which, after gum-salt solution had failed to sustain arterial pressure, transfusion of blood was successful. That this was not due merely to an additive effect of introducing more fluid is indicated by the gradual fall of pressure to the former low level in these cases after the gum-salt injections, and the satisfactory rise after transfusion. It seems probable that what Pike and Coombs (22) have suggested regarding nerve cells is true generally throughout the body—that "injured cells require a better blood supply for their restoration than uninjured cells do for mere maintenance." At least, in the experience of many men who had great opportunities for observation during the War, blood transfusion was found to be the most effective means of dealing with cases of continued low blood pressure, whether due to hemorrhage or shock.

There is the same urgency for using blood early, before serious damage has been done, as there is for using any substitute for blood.

Keith (20) has reported cases of failure of blood transfusion in which there was evidence of escape of fluid just as there was in his failures with gum-salt solution. In one instance 880 c.c. of whole blood increased the recipient's blood volume only 150 c.c. At autopsy in this and in another similar instance, edema of the lungs and more than normally moist tissues were found. To be effective, therefore, blood must be introduced before a low nutrient flow has caused irreparable injury.

As the methods of matching blood, the technic of transfer and the absence of harm to donors become better known, blood transfusion seems certain to become the method of choice for restoring a low blood volume. In hospitals the personnel may be classified in blood groups for emergency purposes. And in military service it is desirable that the lightly wounded and the gassed cases be sent near the shock wards, so that blood may be obtained promptly for those who are in sore need of it.

Precautions to be Observed in Intravenous Injections.—Whether blood or an indifferent fluid is injected, careful attention should be given to the mode of procedure. The possibility of further loss of blood, as the pressure is raised, should be eliminated. The fluid should be introduced slowly, and with little pressure. Zunz and Govaerts (23) have shown that blood transfusion after hemorrhage is effective in restoring normal blood pressure when 40 to 75 minutes are taken to replace about half the blood volume. But if this amount is introduced in 5 to 10 minutes, a marked fall results which may last for hours. And they noted that the deeper and more lasting the circulatory failure before the transfusion, the more slowly must the blood be injected in order to avoid a subsequent drop of pressure.

The fluid should be given warmed to body temperature, or better, slightly above, in order to enter the body warm after passing through the connecting tubes.

If any harmful or unfavorable effects are noticed as the fluid is entering the blood stream, the flow should be checked at once. The amount injected usually need not be great; 500 or 750 c.c. may be given at first, and later 500 c.c. more if circumstances seem to require it. This probably will not restore the blood volume to normal, for as Keith (20, p. 6) and Robertson and Bock (7, p. 224) have shown, the volume is frequently reduced as much as 1500 c.c. or more. Though an intravenous injection may raise the pressure satisfactorily, other and simpler means of increasing the circulating fluid should be continued—such as fluid by mouth and rectum.

On the basis of our Béthune experience, in 1917, Fraser, Hooper and I (24) called attention to the unfavorable prognosis attending continued concentration of the peripheral blood, and to the disappearance or "dilution" of the blood as recovery occurs. Both Keith (20, p. 43) and Lee (15, p. 574) have emphasized the significance of these blood changes, and suggest repeated hemoglobin determinations in order to learn whether "dilution" is occurring and whether the patient, therefore, is on the course towards improvement and recovery.

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CHAPTER XXIII

THE TREATMENT OF SHOCK (*Concluded*)

OPERATION

Operation on a man who has been greatly injured, or who is in shock, or who has been in shock for a considerable period and has to some degree recovered, is likely to be hazardous because a blood pressure barely sustained, or already low, or only recently restored, may be seriously reduced by operative procedures. A number of conditions contribute to this danger, some of which can be avoided.

Anesthesia.—The clinical and experimental evidence that the fall of blood pressure during or after operation in shock is probably chiefly due to ether or chloroform anesthesia has been presented (see p. 104). Sharply contrasted with the effects of these general anesthetics in shock cases is the action of nitrous oxid and oxygen or "gas-oxygen." During his extensive experience as an anesthetist in a casualty clearing station in Flanders, Marshall (1) found in a large series of very severe cases that gas-oxygen anesthesia was followed by no increase of shock whatever. And Bazett (2), who likewise had abundant opportunities to make careful observations, has testified, "One can only say that with nitrous oxid and oxygen anesthesia there is rarely any sign of shock observed. The clinical contrast between cases anesthetized with nitrous oxid and oxygen and those receiving other general anesthetics is enormously in favor of the former." In this connection Dale's observation (3) on the relation of ether and gas-oxygen to histamin shock are highly pertinent. It will be recalled (see p. 163), that he found 10 mgm. of histamin per kilogram necessary to induce shock in the unanesthetized animal, whereas under ether 1 to 2 mgm. were sufficient. But under gas-oxygen, shock could be induced only by giving the dosage required in the unanesthetized state, that is, 10 mgm. Ether and the toxic agent coöperated to bring on the low pressure; with gas-oxygen anesthesia the coöperation was lacking.

Bazett (2) noted that after ether or chloroform there was a concentration of the blood, amounting at times to 20 per cent. With rapid operation under gas-oxygen, however, very slight and only temporary concentration was seen.

Gas-oxygen should be given with great care and by experts in its use. Cattell's observations on the harmful effects of high ratios of nitrous oxid to oxygen (for example, 5 or 4 to 1) have already been described (see p. 109). A ratio of 3 parts nitrous oxid to 1 of oxygen caused no fall of blood pressure whatever. Gwathmey and Yates (4) found in their work on chest cases in battle areas that with a preoperative use of morphin, deep analgesia could be induced and maintained without increasing the ratio above 3 to 1. And Gwathmey (5) has testified that, with proper preliminary medication, complete relaxation of the patient for prolonged periods is easily maintained under gas-oxygen anesthesia. American and British experience during the War led to strong affirmation that in shock cases gas-oxygen is undoubtedly the anesthetic of choice, and this conclusion was accepted by the Interallied Surgical Congress at Paris in 1918.

Whatever the general anesthetic employed, there should be avoidance of deep anesthesia and cyanosis. With the blood volume reduced and the nutrient flow inadequate or bordering on inadequacy, the organism is in danger from oxygen-want. Shutting down the oxygen supply is certain to do harm. As Marshall (6) has remarked, cyanosis during operation causes a shocked man to lose ground which may be extremely hard to recover.

An alternative to a general anesthesia, particularly in operations on the lower extremities, is spinal anesthesia. There is the possibility, however, that through the blocking of tonic vasoconstrictor impulses in the spinal nerves a fall of blood pressure may result. Indeed, Quénu (7) states that this is to be expected. The suggestion has been made that under such circumstances the pressure may be maintained by slow and continuous infusion of a weak solution of adrenalin. Theoretically this is an appropriate mode of procedure, but it is questionable whether there is a special advantage in its use.

A suggestion worthy of further attention comes from Cattell's discovery that in experimental shock intravenous adrenalin injection may prevent for an hour or more the depressive effect of ether on the heart. If experience should prove that this

is a mode of protection applicable in clinical cases, it might remove to some degree the objections to ether as a general anesthetic in shock cases.

Time of Operation.—In 1917 Santy (8) observed 340 cases of non-transportable wounded, in 79 of which the time between the reception of the wound and the surgical treatment was known. The results are tabulated below:

Hours Intervening	Number of Cases	Per cent Mortality
1	10	10
2	9	11
3	8	12
4	11	36
5	9	33
6	12	41
8	8	75
9 and 10	12	75

As the figures show, the mortality was only 11 per cent in the first three hours, it rose to 37 per cent when there was a delay between three and six hours (though infection was not marked until after six hours); and it was 75 per cent from the eighth to the tenth hour. Although during the first hour the cases were not in complete shock, they were in grave condition, anemic and cold. A review of Santy's full description of his cases reveals that in all there were wounds of similar severity. For example, the lesions in the group operated on in the first hour included (1) mashing and pulping of the arm and leg; (2) of the leg and knee and of the forearm (in a diabetic); (3) of the right thigh and left leg; (4) of the thigh in the lower third; (5) of the mid-thigh with laceration of the muscle above; (6) of the leg above the right knee with tearing away of the calf; (7) of the elbow, with wounds of the face, loss of an eye and two large wounds of the thigh; (8) double shattering of the left arm and forearm; (9) destruction of the popliteal space with section of the artery; and (10) laceration of the muscles of both thighs and the calf. Of these 10 cases, 1 died. Amputation was performed in 7 cases (in 2 cases double amputation) with 6 successes. In the last group, operated upon after 9 or 10 hours, the lesions

were (1) extensive laceration of both thighs; (2) smashing of the knee with muscular lesions; (3) crushing of the shoulder; (4) wounds of both thighs with section of the left femoral artery and vein; (5) shattering of the right knee; (6) multiple wounds of the thighs; (7) fracture of the right thigh and the left leg; (8) tearing away of the left arm; (9) muscular destruction of the right thigh; (10) smashing of the leg; (11) of both legs; and (12) of the right thigh. Of these 12 cases, 9 died. There were 6 amputations with only 2 successes.

Santy's observations are sustained by Gatelier (9) who treated 13 serious cases, without waiting, by limited excision of injured tissues or by amputation, and had no deaths.

The excellent results of prompt operation, performed on the severely wounded before the development of secondary shock, have been noted before this time. The great French military surgeon Larrey (10), who followed Napoleon's campaigns, laid down the dictum that crushing wounds of the extremities should be operated upon at once, for that treatment gives the only hope. The figures given by Santy, as already noted (see p. 156), point to action of some agency, which, as time passes, brings on the state of shock and seriously jeopardizes the chances of recovery. The bearing of these observations on the toxic origin of secondary shock is obvious. The crushed and lacerated tissues become not only a source of danger to the body from processes of death taking place in them, but they are most favorable sites for infection. For both reasons, therefore, early clearing away of destroyed tissue, or *débridement,* is a prophylaxis against shock and other damaging conditions.

If secondary shock is already established when the patient, cold and depressed, is brought under surgical care, there is general agreement that simple measures, such as warmth, rest and fluids, should be applied in an attempt to improve his state before operative interference is begun. If, however, there is continued hemorrhage accompanying and augmenting the shock, or if there is rapidly spreading infection (for example, with gas bacilli), operation may be necessary before full recovery has occurred. And, if the surgeon must begin his work thus, a protective transfusion of blood before the anesthetization, or while the wounds are being treated, will tend to keep the blood flow adequate during the most critical time.

The principle involved in the operative treatment of fully developed

secondary shock is the same as that employed for prophylaxis against its development. There must be suppression, as soon as possible, of the traumatized area. Evidence has been given (see p. 156) that this procedure is often the initial step in an extraordinary improvement in the patient's state. At the Interallied Surgical Conference, in 1917, Tuffier (11) declared that we have too long submitted to the doctrine that shock absolutely contra-indicates operation. Experience proves that the exclusion of the focus of injury, by short and radical procedures, causes the symptoms of shock to disappear. And the Conference concluded, "If true shock, without hemorrhage, is severe, if the patient is cold and pulseless, the shock itself must be treated first. It is the same if the operation to be done must be long and difficult. But extensive destruction of parts necessitating amputation indicates operative attack."

Quénu's (7, p. 335) advice is that, in any case, long and complicated operation should be avoided; meticulous surgery is out of place; the principal lesion must be treated quickly and radically, and often less important wounds can be given only simple cleaning.

Precautions to be Observed During Operation.—The relation of cold to shock has been repeatedly emphasized. During operation every effort previously employed to prevent loss of heat should be continued; needless exposure of the body should be avoided. The skin and protective coverings should not be allowed to remain wet, for both by evaporation and by more rapid conduction the escape of heat from the body is thereby promoted. Cavities and wounds should be washed out with warm solutions only. The operating room and the operating table should be warm; even in the rudest circumstances simple arrangements can be made for these desirable conditions.

Again and again in the foregoing pages emphasis has been placed upon the sensitiveness to hemorrhage of the badly injured and the shocked. A small loss of blood, wholly without permanent effect under ordinary circumstances, may cause a calamitous fall of pressure. Special care should be exercised during operation on shock cases not to lose a drop more blood than actually must be lost.

Marshall (1, p. 33) has called attention to the fact that after laparotomy on a man who is, or has been, in shock, a turn of the body laterally causes a sharp drop in blood pressure. He urges that if the back as well as the abdomen has been wounded, it be dealt with before opening the abdomen. Binders or many-tailed

bandages should be applied by lifting the body, not by turning it from side to side.

Abdominal and thoracic viscera should not be exposed or pulled upon more than is absolutely required for the satisfactory performance of the operation. And all tissues should be handled with extreme gentleness.

TREATMENT OF PRIMARY SHOCK

The occurrence of primary shock of clearly nervous origin was so rare in the War that almost no reference has been made to its treatment. It should be dealt with symptomatically—by rest and quiet, and, if the blood pressure remains below the critical level, by measures to increase the blood volume. Every precaution should be taken to avoid the development of secondary shock.

Primary shock due to mortal wounds, or to excessive and sudden hemorrhage, usually offers so little chance for treatment that nothing further need be said concerning it than that the principles developed in the foregoing pages should be applied when there is any hope of their being serviceable.

AFTER CARE

It should be remembered always that the patient who has been in shock and resuscitated, and then operated upon, is in a precarious state. His nervous system has been disturbed not only by the original trauma, but also by the low nutrient flow of blood and by the surgical procedures incidental to operation. Rest is therefore essential, and should be secured, if possible, in sleep. Warmth should likewise be provided, but not to a degree which will induce sweating. It should be remembered that the blood volume has probably been reduced much more than the amount represented by the usual intravenous injection, and that the blood flow will not be normal until the volume is restored to the normal level. Fluids should be continued, therefore, by mouth or rectum until the urine output equals the water intake. Furthermore, the patient should be attentively watched for unfavorable developments and if they arise they should be promptly treated.

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